*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 128:73296

L1 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2000 ACS
RN 200445-63-2 REGISTRY
CN 298-448-Presenilin-2 (Mus musculus isoform PS2s) (9CI) (CA INDEX NAME)
OTHER NAMES:
CN GenBank U57325-derived protein GI 2315276
CN **Presenilin-2 PS2s (mouse PS-2short isoform)**
FS PROTEIN SEQUENCE
MF Unspecified
CI MAN
SR CA
LC STN Files: CA, CAPLUS

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
*** USE 'SQD' OR 'SQIDE' FORMATS TO DISPLAY SEQUENCE ***
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 128:73296

=> fil medl,caplus,biosis,embase,wpids;s (l1 or presenilin 2)

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L2 238 FILE MEDLINE
L3 196 FILE CAPLUS
L4 295 FILE BIOSIS
L5 249 FILE EMBASE
L6 6 FILE WPIDS

TOTAL FOR ALL FILES
L7 984 (L1 OR PRESENILIN 2)

=> s alzheimer and l7

L8 223 FILE MEDLINE
L9 190 FILE CAPLUS
L10 261 FILE BIOSIS
L11 242 FILE EMBASE
L12 6 FILE WPIDS

TOTAL FOR ALL FILES
L13 922 ALZHEIMER AND L7

=> s sequence? and l13

L14 56 FILE MEDLINE
L15 41 FILE CAPLUS
L16 24 FILE BIOSIS
L17 49 FILE EMBASE
L18 5 FILE WPIDS

TOTAL FOR ALL FILES
L19 175 SEQUENCE? AND L13

=> s l19 and (protein or (st george hyslop p? or hyslop p? or rommens j? or fraser p?)/au,in)

'IN' IS NOT A VALID FIELD CODE
L20 56 FILE MEDLINE
L21 39 FILE CAPLUS
L22 19 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L23 45 FILE EMBASE
L24 1 FILE WPIDS

TOTAL FOR ALL FILES
L25 160 L19 AND (PROTEIN OR (ST GEORGE HYSLOP P? OR HYSLOP P? OR ROMMENS
J? OR FRASER P?)/AU,IN)

=> dup rem l25

PROCESSING COMPLETED FOR L25
L26 98 DUP REM L25 (62 DUPLICATES REMOVED)

=> d cbib abs 1-98

L26 ANSWER 1 OF 98 CAPLUS COPYRIGHT 2000 ACS
2000:83101 Document No. 132:136034 Genes for presenilins associated with familial **Alzheimer**'s disease and their use in the identification of agents affecting presenilin interactions with other **proteins**. **St. George-Hyslop, Peter H.**; Rommens, Johanna M.; Fraser, Paul E. (Research and Development Limited Partnership, Can.). U.S. US 6020143 A 20000201, 96 pp., Cont.-in-part of U.S. Ser. No. 592,541. (English). CODEN: USXXAM. APPLICATION: US 1997-888077 19970703. PRIORITY: US 1996-592541 19960126; US 1996-21672 19960705; US 1996-21700 19960712; US 1996-29895 19961108; US 1997-34590 19970102.
AB The identification, isolation, sequencing and characterization of two human presenilin genes, PS-1 and PS-2, mutations in which lead to Familial **Alzheimer**'s Disease, are disclosed. Presenilin gene homologs in

mice, Caenorhabditis elegans and Drosophila melanogaster are also disclosed. Use of the nucleic acids and **proteins** comprising or derived from the presenilins in screening and diagnosing **Alzheimer**'s Disease, identifying and developing therapeutics for treatment of **Alzheimer**'s Disease, in producing cell lines and transgenic animals useful as models of **Alzheimer**'s Disease. Methods for identifying substances that bind to, or modulate the activity of, a presenilin **protein**, functional fragment or variant thereof, or a mutein thereof, and methods for identifying substances that affect the interaction of a presenilin-interacting **protein** with a presenilin **protein**, functional fragment or variant thereof, or a mutein thereof, are further disclosed.

L26 ANSWER 2 OF 98 CAPLUS COPYRIGHT 2000 ACS
2000:54061 Document No. 132:117520 Method for identifying a presenilinase inhibitor for treatment of neurodegenerative diseases. Fechteler, Katja; Haass, Christian; Steiner, Harald (Boehringer Ingelheim Pharma K.-G., Germany). PCT Int. Appl. WO 2000003248 A1 20000120, 91 pp. DESIGNATED STATES: W: AE, AU, BG, BR, CA, CN, CZ, EE, HR, HU, ID, IL, IN, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1999-EP4805 19990708. PRIORITY: EP 1998-112688 19980709.
AB The present invention pertains to methods for identifying a substance capable of reducing or eliminating the activity of the presenilinase wherein a cell or a cell line is cultivated expressing said presenilinase activity and a fusion-**protein** comprising the full-length presenilin 1 or **presenilin 2** and a reporter is measured. The invention is furthermore concerned with substances identifiable with said methods, pharmaceutical compns. comprising said substances and the use of said substances in the manuf. of a medicament for the treatment of neurodegenerative diseases or **Alzheimer**'s disease. Ribozyme **sequences** are reported.

L26 ANSWER 3 OF 98 MEDLINE DUPLICATE 1
2000119333 Document Number: 20119333. Mutational analysis of intrinsic regions of **presenilin 2** that determine its endoproteolytic cleavage and pathological function. Shirotani K; Takahashi K; Araki W; Maruyama K; Tabira T. (Division of Demyelinating Disease and Aging, National Institute of Neuroscience, National Center of Neurology and Psychiatry, 4-1-1 Ogawahigashi, Kodaira, Tokyo 187-8502, Japan.. kshiro@brain.riken.go.jp) . JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Feb 4) 275 (5) 3681-6. Journal code: HIV. ISSN: 0021-9258. Pub. country: United States. Language: English.
AB To investigate the significance of endoproteolytic processing of **presenilin 2** (PS2) on its pathological function, we constructed PS2 cDNAs causing amino acid substitutions or deletions around the cleavage site. We found that a PS2 mutant (Del3) with a 20-amino acid deletion was not endoproteolytically processed, while other PS2s with amino acid substitutions and short deletions were cleaved. Overproduction of all the mutant **proteins** led to a compensatory decrease of endogenous PS1 fragments, but did not affect the amyloid beta peptide X-42/Abeta X-40 ratio without the familial **Alzheimer**'s disease mutation. The Del3 mutant did not exhibit significant deficits in gamma-secretase activity. The turnover rate of the Del3 holoprotein was the same as that of full-length PS2. These data suggest that the determinants of the PS2 cleavage site reside within a large region and that the pathological function of PS2 is exerted by familial **Alzheimer**'s disease mutations not related to the cleavage of

holoproteins. We also found that PS2 with an 18-amino acid deletion at the C-terminal end was not processed. Its overexpression led neither to diminished accumulation of endogenous PS1 fragments nor to increased production of amyloid beta peptide X-42. The C-terminal end of PS2 seems to possess the signal for entry into the processing pathway.

L26 ANSWER 4 OF 98 MEDLINE DUPLICATE 2
2000119269 Document Number: 20119269. The transmembrane aspartates in presenilin 1 and 2 are obligatory for gamma-secretase activity and amyloid beta-**protein** generation. Kimberly W T; Xia W; Rahmati T; Wolfe M S; Selkoe D J. (Department of Neurology, Harvard Medical School and Center for Neurologic Diseases, Brigham and Women's Hospital, Boston, Massachusetts 02115, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Feb 4) 275 (5) 3173-8. Journal code: HIV. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB The discovery that a deficiency of presenilin 1 (PS1) decreases the production of amyloid beta-**protein** (Abeta) identified the presenilins as important mediators of the gamma-secretase cleavage of beta-amyloid precursor **protein** (APP). Recently, we found that two conserved transmembrane (TM) aspartates in PS1 are critical for Abeta production, providing evidence that PS1 either functions as a required diaspartyl cofactor for gamma-secretase or is itself gamma-secretase. **Presenilin 2** (PS2) shares substantial **sequence** and possibly functional homology with PS1. Here, we show that the two TM aspartates in PS2 are also critical for gamma-secretase activity, providing further evidence that PS2 is functionally homologous to PS1. Cells stably co-expressing TM Asp --> Ala mutations in both PS1 and PS2 show further accumulation of the APP-derived gamma-secretase substrates, C83 and C99. The production of Abeta is reduced to undetectable levels in the conditioned media of these cells. Furthermore, endoproteolysis of the exogenous Asp mutant PS2 is absent, and endogenous PS1 C-terminal fragments are diminished to undetectable levels. Therefore, the co-expression of PS1 and PS2 TM Asp --> Ala mutants suppresses the formation of any detectable PS1 or PS2 heterodimeric fragments and essentially abolishes the production of Abeta. These results explain the residual Abeta production seen in PS1-deficient cells and demonstrate the absolute requirement of functional presenilins for Abeta generation. We conclude that presenilins, and their TM aspartates in particular, are attractive targets for lowering Abeta therapeutically to prevent **Alzheimer**'s disease.

L26 ANSWER 5 OF 98 CAPLUS COPYRIGHT 2000 ACS
1999:753344 Document No. 132:11416 **Presenilin-2** splice variants from human nerve cells cultured under stress and use of the system for drug screening. Takagi, Tsutomu; Sato, Naoya; Tohyama, Masaya (Tanabe Seiyaku Co., Ltd., Japan). PCT Int. Appl. WO 9960122 A1 19991125, 41 pp. DESIGNATED STATES: W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (Japanese). CODEN: PIXXD2. APPLICATION: WO 1999-JP2627 19990520. PRIORITY: JP 1998-139408 19980521.

AB Three novel **presenilin-2** splice variants are obsd. in the cultured human neuroblastoma cell line SK-N-SH under hypoxia condition, or further treated with H2O2 or stimulated with .beta.-amyloid.

The splice variants have also been be obsd. in patients with **Alzheimer**'s disease. The system can be used for screening therapeutics or prophylactics for the central nervous system diseases such as **Alzheimer**'s disease by detg. whether a substance can block the hypoxia-induced splice variants.

L26 ANSWER 6 OF 98 CAPLUS COPYRIGHT 2000 ACS
1999:468603 Document No. 131:98493 Replication defective herpes virus (HSV-2) vector and its use in the treatment of neurological disorders. Aurelian, Laure; Calton, Gary; Kulka, Michael (Aurx, Inc., USA). PCT Int. Appl. WO 9936513 A1 19990722, 36 pp. DESIGNATED STATES: W: AU, CA, JP, KR; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US921 19990115. PRIORITY: US 1998-9531 19980120.

AB The invention relates to a replication defective herpes virus (HSV-2) which has been sufficiently deleted in the gene (ICP10) coding for the large subunit of ribonucleotide reductase (RR1) to render the produced **proteins** defective in their function. ICP10 codes for RR1 and a serine/threonine **protein** kinase, which is required for the prodn. of the viral IE **proteins** ICP4 and ICP27 that regulate the expression of all other HSV genes and RR1. Since the virus does not have ribonucleotide reductase activity nor **protein** kinase activity, the virus cannot replicate itself nor express other viral genes, and the **sequences** which code for the small RR subunit (RR2) may be deleted in order to provide addnl. space for foreign genes. The replication defective virus may have a therapeutic gene **sequence** inserted in the place of these deleted or partially deleted genes. The insertion of a gene for a neurotrophic factor may be driven by an appropriate promoter and may be used in the treatment of neurol. disorders such as Parkinson's disease, **Alzheimer**'s disease, diabetic neuropathy, and neuropathic pain resulting from nerve injury.

L26 ANSWER 7 OF 98 CAPLUS COPYRIGHT 2000 ACS
1999:454280 Document No. 131:86462 Presenilin **protein** interactions. **St. George-Hyslop, Peter H.**; Fraser, Paul E. (Can.). PCT Int. Appl. WO 9935501 A1 19990715, 40 pp. DESIGNATED STATES:
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-CA18 19990108. PRIORITY: US 1998-70948 19980109.

AB Disclosed is a method for identifying substances that alter the interaction of a presenilin **protein** with a presenilin-binding **protein**, including contacting at least the interacting domain of a presenilin **protein** to a presenilin-binding **protein** in the presence of a test substance, and measuring the interaction of the presenilin **protein** and the presenilin-binding **protein**. Also disclosed is a method for identifying substances that modulate the nuclear translocation of an armadillo **protein**, including providing a culture of cells that express the armadillo **protein** and a mutant presenilin **protein**, or a functional fragment thereof that binds an armadillo **protein**; contacting the culture with a test substance; inducing nuclear translocation of the armadillo **protein** in the cells; and measuring levels of nuclear armadillo

protein as compared to a control as an indication of modulatory activity of the test substance. Further disclosed is a method for screening individuals for presenilin alleles assocd. with **Alzheimer**'s Disease or related disorder, including obtaining cells from an individual to be tested for **Alzheimer**'s Disease or a related disorder; inducing nuclear translocation of an armadillo **protein** in the cells, and measuring levels of the nuclear armadillo **protein** as compared to a control as an indication of the presence or absence of presenilin alleles assocd. with **Alzheimer**'s Disease or a related disorder.

L26 ANSWER 8 OF 98 CAPLUS COPYRIGHT 2000 ACS

1999:297445 Document No. 130:320859 Peptides capable of inhibiting the interaction between presenilins and the .beta.-amyloid peptide or its precursor. Czech, Christian; Mercken, Luc; Pradier, Laurent; Reboul-Becquart, Soline (Rhone-Poulenc Rorer S.A., Fr.). PCT Int. Appl. WO 9921886 A1 19990506, 101 pp. DESIGNATED STATES: W: AL, AT, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (French). CODEN: PIXXD2. APPLICATION: WO 1998-FR2278 19981023. PRIORITY: FR 1997-13384 19971024; US 1998-95671 19980807.

AB Peptides that can inhibit the interaction of presenilins 1 and 2 with .beta.-amyloid **protein** or .beta.-amyloid precursor are described for therapeutic use. These peptides are derived from the domains of the presenilins and the amyloid **protein** involved in the interaction and may be of use in inhibiting amyloid plaque formation in treatment of **Alzheimer**'s disease (no data). Methods of screening for peptides or peptidomimetics inhibiting the interaction are also described. The domains involved in the interaction of the two **proteins** were mapped using deletion derivs. manufd. by expression of the cloned genes. The N-terminal region of **presenilin 2** was found to be important in the interaction. A microtiter plate assay using an immobilized N-terminal 42-amino acid fragment of the .beta.-amyloid is described.

L26 ANSWER 9 OF 98 CAPLUS COPYRIGHT 2000 ACS

1999:733863 Document No. 131:347538 Genetic **sequences** and **proteins** related to **Alzheimer**'s disease. **St. George-Hyslop, Peter H.**; Rommens, Johanna M.; Fraser, Paul E. (The Hospital for Sick Children, HSC Research and Development Limited Partnership, Can.; The Governing Council of the University of Toronto). U.S. US 5986054 A 19991116, 131 pp., Cont.-in-part of U.S. Ser. No. 509,359. (English). CODEN: USXXAM. APPLICATION: US 1996-592541 19960126. PRIORITY: US 1995-431048 19950428; US 1995-496841 19950628; US 1995-509359 19950731.

AB The present invention describes the identification, isolation and cloning of two human presenilin genes, PS-1 and PS-2, mutations in which lead to familial **Alzheimer**'s disease. The **Alzheimer**'s related membrane **protein** (ARMP) gene (or presenilin I (PSI)) gene was isolated, cloned and **sequenced** from within the AD3 region on chromosome 14q4.3. In addn., direct sequencing of RT-PCR products spanning this 3.0 kb cDNA transcript isolated from affected members of at least 8 large pedigrees linked to chromosome 14, has led to the discovery of missense mutations in each of these different pedigrees. These mutations are absent in normal chromosomes. Also identified are presenilin homolog genes in mice, Caenorhabditis elegans (SEL-12) and Drosophila melanogaster (DmPS). Transcripts and products of these genes are useful in detecting and diagnosing **Alzheimer**'s disease,

developing therapeutics for treatment of **Alzheimer**'s disease, as well as the isolation and manuf. of the **protein**, and the constructions of transgenic animals expressing the mutant genes.

L26 ANSWER 10 OF 98 WPIDS COPYRIGHT 2000 DERWENT INFORMATION LTD
AN 1999-430307 [36] WPIDS
AB WO 9934670 A UPAB: 19990908
NOVELTY - A gene mutant animal having a non-human mutant presenilin gene, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a similar gene mutant animal who has:

(a) a gene in which the amino-acid numbers substituted can be 1 or more of 79, 82, 96, 115, 120, 135, 139, 143, 146, 163, 209, 213, 231, 235, 246, 250, 260, 263, 264, 267, 269, 280, 285, 286, 290, 318, 384, 392, 410, 426 and 436, with corresponding N-terminals being e.g. A79V, V82L, A426 and P436S, particularly by replacing isoleucine of No. 213 by other amino-acid especially threonine; or

(b) who has a mutant **presenilin-2** gene which is a DNA encoding a mutant **protein** with some amino-acids of the **presenilin-2 protein**, particularly on the amino-acid numbers 141 and/or 436 (N-terminals being N141I and/or M239V);

(2) a plasmid containing the whole or a part of the DNA **sequence** of a mutated presenilin-1 gene;

(3) a chromosomal DNA containing the exon 8 of mutated presenilin-1 gene that encodes the substitution-mutated presenilin-1 **protein**;

(4) a similar plasmid containing a cDNA of mutated presenilin-1 gene or an introduced DNA with a base **sequence** of the whole or mutated part of the chromosomal DNA corresponding to the Sau3Ai position;

(5) a gene containing a DNA encoding a mutant mouse presenilin-1 **protein** or variant;

(6) a plasmid containing a DNA encoding the mutant presenilin-1 **protein** and loxP-sandwiched neomycin-expressing unit;

(7) an embryo inserted with the DNA-containing (homologously recombined) plasmid, which can be obtained by using the recombinant plasmid;

(8) first or subsequent generation cultured cells obtained by culturing the isolated cells or tissue culture;

(9) a method for producing the gene mutant animal from the embryo;

(10) a method for expressing mutant presenilin-1 **protein** from the gene mutant animal;

(11) a method for evaluating a substance for the treatment and/or prevention of **Alzheimer**'s diseases by administering it to a gene mutant animal and compared results obtained by using a control;

(12) an evaluation method of therapy and/or prevention of **Alzheimer**'s diseases by in vitro cell culturing of the cultured cells with or without the test compound;

(13) a method for diagnosis of the possibility of onset of **Alzheimer**'s diseases by using the partial base **sequence** of gene encoding the OS-2 type mutant presenilin-1 **protein**;

(14) a substance selected by the evaluation method for treating and/or preventing **Alzheimer**'s diseases;

(15) an agent for treating and/or preventing **Alzheimer**'s diseases contains (14) as an active ingredient;

(16) another gene mutant animal, particularly a mouse, who has a gene encoding the amyloid precursor **protein** and can overexpress

amyloid beta **protein**; and

(17) a gene mutant mouse containing the above mutant gene.

USE - The gene mutant animals e.g. mice can be used as model animals for the study of human **Alzheimer**'s diseases and to screen and evaluate substances as candidates for prevention and/or therapy of **Alzheimer**'s diseases in patients (claimed). They can over-produce amyloid beta **protein** by the presenilin-1 gene to cause nerve cell death or peeling off in the hippocampus earlier.

ADVANTAGE - Such animals are being pathologically close to human patients with **Alzheimer**'s diseases.

DESCRIPTION OF DRAWING(S) - Process of producing a plasmid pmx retaining a part of exon 8 of mouse presenilin-1 gene, with illustration of the OS-2 mutation introduced position obtained by the site-specific mutation introduction method.

Dwg.2/8

L26 ANSWER 11 OF 98 MEDLINE DUPLICATE 3

2000044792 Document Number: 20044792. The influence of endoproteolytic processing of familial **Alzheimer**'s disease **presenilin 2** on abeta42 amyloid peptide formation. Jacobsen H; Reinhardt D; Brockhaus M; Bur D; Kocyba C; Kurt H; Grim M G; Baumeister R; Loetscher H.

(Pharma Division, Preclinical Central Nervous System Research, CH-4070 Basel, Switzerland.. helmut.jacobsen@roche.com) . JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Dec 3) 274 (49) 35233-9. Journal code: HIV. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Mutant presenilins (PS) contribute to the pathogenesis of familial **Alzheimer**'s disease (FAD) by enhancing the production of Abeta42 from beta-amyloid precursor **protein**. Presenilins are endoproteolytically processed to N-terminal and C-terminal fragments, which together form a stable 1:1 complex. We have mapped the cleavage site in the PS2 **protein** by direct sequencing of its C-terminal fragment isolated from mouse liver. Three different N-terminal residues were identified starting at Val-299, Thr-301, and Leu-307 that correspond closely to the previously described N termini of the C-terminal fragment of human PS1. Mutational analysis of the PS2 cleavage site indicates that the principal endoproteolytic cleavage occurs at residues Met-298/Val-299 and that the N terminus is subsequently modified by secondary proteolytic cleavages. We have generated cleavage defective PS2 constructs, which accumulate exclusively as full-length polypeptides in transfected Neuro2a cells. Functional analysis of such cleavage defective PS2 carrying the FAD mutation Asn-141 --> Ile showed that its Abeta42 producing activity was strongly reduced compared with cleavage-competent FAD PS2. In contrast, cleavage defective PS2 was active in rescuing the egg-laying defect of a sel-12 mutant in Caenorhabditis elegans. We conclude that PS2 endoproteolytic cleavage is not an absolute requirement for its activities but may rather selectively enhance or stabilize its functions.

L26 ANSWER 12 OF 98 MEDLINE DUPLICATE 4

1999367502 Document Number: 99367502. Membrane topology of **Alzheimer**'s disease-related presenilin 1. Evidence for the existence of a molecular species with a seven membrane-spanning and one membrane-embedded structure. Nakai T; Yamasaki A; Sakaguchi M; Kosaka K; Mihara K; Amaya Y; Miura S. (Radioisotope Research Center, Yokohama City University School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama 236-0004, Japan.) JOURNAL OF

BIOLOGICAL CHEMISTRY, (1999 Aug 13) 274 (33) 23647-58. Journal code: HIV.
ISSN: 0021-9258. Pub. country: United States. Language: English.

AB A significant member of early-onset familial type of **Alzheimer's** disease cases has been shown to be caused by dominant mutations in either of the two genes encoding presenilin 1 (PS1) and **presenilin 2** (PS2). These two **proteins** are highly homologous to each other and have been reported to be mainly localized to the membranes of intracellular compartments such as the endoplasmic reticulum. Information about the membrane topological structures of these **proteins** is indispensable for understanding their physiological and pathological roles. Although several models have been proposed previously, their precise membrane topologies remain unknown. In this study, we examined this issue in detail by expressing a series of C-terminally deleted PS1 mutants fused to the hydrophilic portion of Escherichia coli leader peptidase in vitro using a reticulocyte lysate in the presence of microsomal membranes. Our results predict that PS1 exists mainly in a seven membrane-spanning structure with its C-terminal end exposed to the luminal space. This was also confirmed by expressing these fusion **proteins** in cultured cells. We further showed that a ninth hydrophobic segment is tightly bound to the membrane without spanning it. Based on the above observations, we propose a novel "seven membrane-spanning and one membrane-embedded" topological model for presenilins.

L26 ANSWER 13 OF 98 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 5

2000:33231 Document No.: PREV200000033231. Amyloidogenic function of the **Alzheimer's** disease-associated presenilin 1 in the absence of endoproteolysis. Steiner, Harald; Romig, Helmut; Pesold, Brigitte; Philipp, Uwe; Baader, Miriam; Citron, Martin; Loetscher, Hansruedi; Jacobsen, Helmut; Haass, Christian (1). (1) Laboratory for Alzheimer's Disease Research, Department of Biochemistry, Adolf Butenandt-Institute, Ludwig-Maximilians-University, 80336, Munich Germany. Biochemistry, (Nov. 2, 1999) Vol. 38, No. 44, pp. 14600-14605. ISSN: 0006-2960. Language: English. Summary Language: English.

AB **Alzheimer's** disease (AD) is characterized by the invariant accumulation of senile plaques predominantly composed of the pathologically relevant 42-amino acid amyloid beta-peptide (Abeta42). The presenilin (PS) **proteins** play a key role in Abeta generation. FAD-associated mutations in PS1 and PS2 enhance the production of Abeta42, and PS1 is required for physiological Abeta production, since a gene knockout of PS1 and dominant negative mutations of PS1 abolish Abeta generation. PS **proteins** undergo endoproteolytic processing, and current evidence indicates that fragment formation may be required for the amyloidogenic function of PS. We have now determined the **sequence** requirements for endoproteolysis of PS1. Mutagenizing amino acids at the previously determined major cleavage site (amino acid 298) had no effect on PS1 endoproteolysis. In contrast, mutations or deletions at the additional cleavage site around amino acid 292 blocked endoproteolysis. The uncleavable PS1 derivatives accumulated as full-length **proteins** and replaced the endogenous PS1 **proteins**. In contrast to the previously described aspartate mutations within transmembrane domains 6 and 7, the uncleaved PS1 variants do not act as dominant negative inhibitors of Abeta production. Moreover, when a FAD-associated mutation (M146L) was combined with a mutation blocking endoproteolysis, Abeta42 production still reached pathological levels. These data therefore demonstrate that endoproteolysis of presenilins is not an absolute prerequisite for the amyloidogenic function of PS1. These data also show that accumulation of the PS1 holoprotein is not associated

with the pathological activity of PS1 mutations as suggested previously.

L26 ANSWER 14 OF 98 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1999172975 EMBASE Evidence that intramolecular associations between presenilin domains are obligatory for endoproteolytic processing. Saura C.A.; Tomita T.; Davenport F.; Harris C.L.; Iwatsubo T.; Thinakaran G..
G.
Thinakaran, Dept. of Neurobiology, University of Chicago, Knapp Research Center, 924 E. 57th St., Chicago, IL 60637, United States. gopal@uchicago.edu. Journal of Biological Chemistry 274/20 (13818-13823) 14 May 1999.
Refs: 43.
ISSN: 0021-9258. CODEN: JBCHA3. Pub. Country: United States. Language: English. Summary Language: English.
AB Mutations in genes encoding presenilins (PS1 and PS2) cosegregate with the
majority of early onset cases of familial **Alzheimer**'s disease. PS1 and PS2 are polytopic membrane **proteins** that undergo endoproteolytic cleavage to generate stable NH2- and COOH-terminal derivatives (NTF and CTF, respectively). Several lines of evidence suggest
that the endoproteolytic derivatives are likely the functional units of PS
in vivo. In the present report, we examine the disposition of PS NTF and CTF assemblies in stable mouse N2a neuroblastoma cell lines expressing human PS polypeptides. We show that exogenous expression of PS1 NTFs neither assemble with endogenous CTF nor exhibit dominant negative inhibitory effects on the endogenous PS1 cleavage and the accumulation of derivatives. In cells co-expressing PS1 and PS2, PS1- and PS2-derived fragments do not form mixed assemblies. In contrast, cells expressing a chimeric PS1/PS2 polypeptide form stable PS1 NTF-PS2 CTF assemblies. Moreover, expression of chimeric PS1/PS2 polypeptides harboring a familial
early onset AD-linked mutation (M146L) elevates the production of A.beta.42 peptides. Our results provide evidence that assembly of structural domains contained within NH2- and COOH-terminal regions of PS occur prior to endoproteolyric cleavage.

L26 ANSWER 15 OF 98 MEDLINE
1999194751 Document Number: 99194751. Direct interaction of **Alzheimer**'s disease-related presenilin 1 with armadillo **protein** p0071. Stahl B; Diehlmann A; Sudhof T C. (Max Planck Institute for Experimental Medicine, 37075 Gottingen, Germany.. stahl@mail.mpiem.gwdg.de) . JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Apr 2) 274 (14) 9141-8. Journal code: HIV. ISSN: 0021-9258. Pub. country: United
States. Language: English.
AB **Alzheimer**'s disease-related presenilins are thought to be involved in Notch signaling during embryonic development and/or cellular differentiation. **Proteins** mediating the cellular functions of the presenilins are still unknown. We utilized the yeast two-hybrid system
to identify an interacting armadillo **protein**, termed p0071, that binds specifically to the hydrophilic loop of presenilin 1. In vivo, the presenilins constitutively undergo proteolytic processing, forming two stable fragments. Here, we show that the C-terminal fragment of presenilin
1 directly binds to p0071. Nine out of 10 armadillo repeats in p0071 are essential for mediating this interaction. Since armadillo **proteins**, like beta-catenin and APC, are known to participate in cellular signaling, p0071 may function as a mediator of presenilin 1 in signaling

events.

L26 ANSWER 16 OF 98 MEDLINE
1999277363 Document Number: 99277363. A novel **presenilin-2** splice variant in human **Alzheimer**'s disease brain tissue. Sato N; Hori O; Yamaguchi A; Lambert J C; Chartier-Harlin M C; Robinson P A; Delacourte A; Schmidt A M; Furuyama T; Imaizumi K; Tohyama M; Takagi T. (Tanabe Seiyaku Co., Ltd., Department of Anatomy and Neuroscience, Osaka University Medical School, Suita, Japan.) JOURNAL OF NEUROCHEMISTRY, (1999 Jun) 72 (6) 2498-505. Journal code: JAV. ISSN: 0022-3042. Pub. country: United States. Language: English.

AB Mutations in the presenilin-1 (PS-1) and **presenilin-2** (PS-2) genes account for the majority of cases of early-onset familial **Alzheimer**'s disease (AD). Alternative splicing forms of the PS-1 and PS-2 gene products have previously been reported in fibroblast and brain tissue from both familial and sporadic AD patients, as well as from normal tissues and cell lines. We demonstrate here unusual alternative splicing of the PS-2 gene that leads to the generation of mRNA lacking exon 5 in human brain tissue. This product was more frequently detected in brain tissue from sporadic AD patients (70.0%; 21 of 30) than from normal age-matched controls (17.6%; three of 17). In cultured neuroblastoma cells, this splice variant was generated in hypoxia but not under other forms of cellular stress. Hypoxia-mediated induction of this splice variant was blocked by pretreatment of neuroblastoma cells with the **protein** synthesis inhibitor cycloheximide or antioxidants such as N-acetylcysteine and diphenyl iodonium, suggesting that hypoxia-mediated oxidant stress might, at least in part, underlie the alternative splicing of PS-2 mRNA through de novo **protein** synthesis. Furthermore, the stable transfectants of this splice variant produced the N-terminal part of PS-2 **protein** (15 kDa) and were more susceptible to cellular stresses than control transfectants. These results suggest the possibility that altered presenilin gene products in stress conditions may also participate in the pathogenesis of AD.

L26 ANSWER 17 OF 98 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1999264896 EMBASE Localisation of **presenilin 2** in human and rodent pancreatic islet .beta.-cells; Met239Val **presenilin 2** variant is not associated with diabetes in man. Jaikaran E.T.A.; Marcon G.; Levesque L.; **St George-Hyslop P.**; **Fraser P.E.** ; Clark A.. E.T.A. Jaikaran, Diabetes Research Laboratories, Oxford, United Kingdom. emma@drl.ox.ac.uk. Journal of Cell Science 112/13 (2137-2144) 1999.
Refs: 52.
ISSN: 0021-9533. CODEN: JNCSAI. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Mutations in presenilin 1 and 2 are causative factors for early onset familial **Alzheimer**'s disease and possible roles for presenilins include **protein** trafficking, regulation of apoptosis and/or calcium homeostasis. **Presenilin 2** mRNA is expressed in brain, muscle and pancreas but the role of pancreatic **presenilin 2** and its relationship to diabetes are unknown. **Presenilin 2** immunoreactivity was localised in human and rodent pancreas to islet cells and found in granules of .beta.-cells. **Presenilin 2** was identified in primitive islet and duct cells of human foetal pancreas and in proliferating exocrine duct cells in human pancreatitis but not found in islet amyloid deposits in Type 2 diabetic subjects. Full length, .apprx. 50 kDa, and the .apprx. 30 kDa N-terminal fragment of **presenilin 2** were identified by western blotting in extracted rodent pancreas but only the 30 kDa fragment was detected in

mouse islets and human insulinoma. Postmortem pancreatic morphology was normal in a subject with the **presenilin 2** Met239Val variant and early onset familial **Alzheimer**'s disease. Oral glucose tolerance tests on subjects with the **presenilin 2** Met239Val mutation unaffected by early onset familial **Alzheimer**'s disease (mean age 35 years) and on their first-degree relatives without the mutation demonstrated no evidence of glucose intolerance or increased proinsulin secretion. PS2 is a novel .beta.-cell **protein** with potential roles in development or **protein** processing but pancreatic islet structure and function appear to be unaffected by the Met239Val mutation.

L26 ANSWER 18 OF 98 MEDLINE DUPLICATE 6

1999196495 Document Number: 99196495. Characterization of detergent-insoluble complexes containing the familial **Alzheimer**'s disease-associated presenilins. Parkin E T; Hussain I; Karran E H; Turner A J; Hooper N M. (School of Biochemistry and Molecular Biology, University of Leeds, England, UK.) JOURNAL OF NEUROCHEMISTRY, (1999 Apr) 72 (4) 1534-43. Journal code: JAV. ISSN: 0022-3042. Pub. country: United States. Language: English.

AB Many cases of early-onset familial **Alzheimer**'s disease have been linked to mutations within two genes encoding the **proteins** presenilin-1 and **presenilin-2**. The presenilins are 48-56-kDa **proteins** that can be proteolytically cleaved to generate an N-terminal fragment (approximately 25-35 kDa) and a C-terminal fragment (approximately 17-20 kDa). The N- and C-terminal fragments of presenilin-1, but not full-length presenilin-1, were readily detected in both human and mouse cerebral cortex and in neuronal and glioma cell lines. In contrast, **presenilin-2** was detected almost exclusively in cerebral cortex as the full-length molecule with a molecular mass of 56 kDa. The association of the presenilins with detergent-insoluble, low-density membrane microdomains, following the isolation of these structures from cerebral cortex by solubilization in Triton X-100 and subsequent sucrose density gradient centrifugation, was also examined. A minor fraction (10%) of both the N- and C-terminal fragments of presenilin-1 was associated with the detergent-insoluble, low-density membrane microdomains, whereas a considerably larger proportion of full-length **presenilin-2** was present in the same membrane microdomains. In addition, a significant proportion of full-length **presenilin-2** was present in a high-density, detergent-insoluble cytoskeletal pellet enriched in beta-actin. The presence of the presenilins in detergent-insoluble, low-density membrane microdomains indicates a possible role for these specialized regions of the membrane in the lateral separation of **Alzheimer**'s disease-associated **proteins** within the lipid bilayer and/or in the distinct functions of these **proteins**.

L26 ANSWER 19 OF 98 MEDLINE DUPLICATE 7

1999145560 Document Number: 99145560. Phosphorylation of **presenilin -2** regulates its cleavage by caspases and retards progression of apoptosis. Walter J; Schindzielorz A; Grunberg J; Haass C. (Central Institute of Mental Health, Department of Molecular Biology, J5, 68159 Mannheim, Germany.) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1999 Feb 16) 96 (4) 1391-6. Journal code: PV3. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB Mutations within the **Presenilin-2** (PS-2) gene are associated with early onset familial **Alzheimer**'s disease. The gene encodes a polytopic transmembrane **protein** that undergoes endoproteolytic processing resulting in the generation of N-terminal and C-terminal fragments (CTFs). PS-2 is also cleaved by proteases of the

caspase family during apoptotic cell death. CTFs of PS-2 were shown to inhibit apoptosis, suggesting an important role in the regulation of programmed cell death. Recently, we found that the CTF of PS-2 is phosphorylated in vivo. We mapped the in vivo phosphorylation sites of PS-2 to serine residues 327 and 330, which are localized immediately adjacent to the cleavage sites of caspases after aspartate residues 326 and 329. Phosphorylation of PS-2 inhibits its cleavage by caspase-3. This effect can be mimicked by substitutions of serines 327 and 330 by aspartate or glutamate. In addition, the uncleavable form of PS-2 CTF was found to enhance its antiapoptotic properties, leading to a slower progression of apoptosis. These results demonstrate that PS-2 cleavage as well as its function in apoptosis can be regulated by **protein** phosphorylation. Alterations in the phosphorylation of PS-2 may therefore promote the pathogenesis of AD by affecting the susceptibility of neurons to apoptotic stimuli.

L26 ANSWER 20 OF 98 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1999355031 EMBASE Apoptotic activities of wild-type and **Alzheimer**'s disease-related mutant presenilins in Drosophila melanogaster. Ye Y.; Fortini M.E.. M.E. Fortini, Department of Genetics, Stellar-Chance Laboratories, Univ. of Pennsylvania Sch. of Med., 422 Curie Boulevard, Philadelphia, PA 19104, United States. fortini@mail.med.upenn.edu.
Journal of Cell Biology 146/6 (1351-1364) 20 Sep 1999.
Refs: 58.
ISSN: 0021-9525. CODEN: JCLBA3. Pub. Country: United States. Language: English. Summary Language: English.
AB Mutant human presenilins cause early-onset familial **Alzheimer**'s disease and render cells susceptible to apoptosis in cultured cell models.
We show that loss of presenilin function in Drosophila melanogaster increases levels of apoptosis in developing tissues. Moreover, overexpression of presenilin causes apoptotic and neurogenic phenotypes resembling those of Presenilin loss-of-function mutants, suggesting that presenilin exerts a dominant negative effect when expressed at high levels. In Drosophila S2 cells, Psn overexpression leads to reduced Notch receptor synthesis affecting levels of the intact .apprx.300-kD precursor and its .apprx.120-kD processed COOH-terminal derivatives. Presenilin-induced apoptosis is cell autonomous and can be blocked by constitutive Notch activation, suggesting that the increased cell death is due to a developmental mechanism that eliminates improperly specified cell types. We describe a genetic model in which the apoptotic activities of wild-type and mutant presenilins can be assessed, and we find that **Alzheimer**'s disease-linked mutant presenilins are less effective at inducing apoptosis than wild-type presenilin.

L26 ANSWER 21 OF 98 MEDLINE DUPLICATE 8
1999296618 Document Number: 99296618. A myristoylated calcium-binding **protein** that preferentially interacts with the **Alzheimer**'s disease **presenilin 2 protein**. Stabler S M; Ostrowski L L; Janicki S M; Monteiro M J. (Medical Biotechnology Center and Department of Neurology, University of Maryland, Baltimore, Maryland 21201, USA.) JOURNAL OF CELL BIOLOGY, (1999 Jun 14) 145 (6) 1277-92.
Journal code: HMV. ISSN: 0021-9525. Pub. country: United States. Language: English.
AB It is well established that mutations in the presenilin 1 and 2 genes cause the majority of early onset **Alzheimer**'s disease (AD).

However, our understanding of the cellular functions of the **proteins** they encode remains rudimentary. Knowledge of **proteins** with which the presenilins interact should lead to a better understanding of presenilin function in normal and disease states. We report here the identification of a calcium-binding **protein**, calmyrin, that interacts preferentially with **presenilin 2** (PS2). Calmyrin is myristoylated, membrane-associated, and colocalizes with PS2 when the two **proteins** are overexpressed in HeLa cells. Yeast two-hybrid liquid assays, affinity chromatography, and coimmunoprecipitation experiments confirm binding between PS2 and calmyrin. Functionally, calmyrin and PS2 increase cell death when cotransfected into HeLa cells. These results allude to several provocative possibilities for a dynamic role of calmyrin in signaling, cell death, and AD.

L26 ANSWER 22 OF 98 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1999246610 EMBASE Presenilins interact with Rab11, a small GTPase involved in the regulation of vesicular transport. Dumanchin C.; Czech C.; Campion D.; Cuif M.H.; Poyot T.; Martin C.; Charbonnier F.; Goud B.; Pradier L.; Frebourg T.. T. Frebourg, INSERM EPI 9906, Faculte de Medecine et de Pharmacie, 22 Boulevard de Gambetta, 76183 Rouen, France. frebourg@chu-rouen.fr. Human Molecular Genetics 8/7 (1263-1269) 1999. Refs: 56.
ISSN: 0964-6906. CODEN: HMGEE5. Pub. Country: United Kingdom. Language: English. Summary Language: English.
AB Presenilin 1 (PS1) mutations account for the majority of early-onset dominant cases of familial **Alzheimer**'s disease. Presenilins (PSs) are located in many intracellular compartments such as the endoplasmic reticulum, Golgi apparatus, nuclear region and vesicular structures. These **proteins** include from seven to nine putative transmembrane domains, with the N- and C-terminal ends and a large hydrophilic loop orientated towards the cytoplasm. We report an interaction between the human PS1 or PS2 hydrophilic loop and Rab11, a small GTPase belonging to the Ras-related superfamily. Interaction domains were mapped to codons 374-400 for PS1 and to codons 106-179 for Rab11, a region including the fourth GTP-binding domain. Considering the implication of Rab **proteins** in vesicular transport pathways, the PS-Rab11 interaction suggests that PSs might be involved in amyloid precursor **protein** vesicular routing.

L26 ANSWER 23 OF 98 MEDLINE DUPLICATE 9
1999155075 Document Number: 99155075. Presenilins interact with armadillo **proteins** including neural-specific plakophilin-related **protein** and beta-catenin. Levesque G; Yu G; Nishimura M; Zhang D M; Levesque L; Yu H; Xu D; Liang Y; Rogaeva E; Ikeda M; Duthie M; Murgolo N; Wang L; VanderVere P; Bayne M L; Strader C D; **Rommens J M; Fraser P E; St. George-Hyslop P.** (Centre for Research in Neurodegenerative Diseases, Department of Medicine (Neurology), University of Toronto, and Toronto Hospital, Ontario, Canada.) JOURNAL OF NEUROCHEMISTRY, (1999 Mar) 72 (3) 999-1008. Journal code: JAV. ISSN: 0022-3042. Pub. country: United States. Language: English.
AB Missense substitutions in the presenilin 1 (PS1) and **presenilin 2** (PS2) **proteins** are associated with early-onset familial **Alzheimer**'s disease. We have used yeast-two-hybrid and coimmunoprecipitation methods to show that the large cytoplasmic loop

domains of PS1 and PS2 interact specifically with three members of the armadillo **protein** family, including beta-catenin, p0071, and a novel neuronal-specific armadillo **protein**--neural plakophilin-related armadillo **protein** (NPRAP). The PS1:NPRAP interaction occurs between the arm repeats of NPRAP and residues 372-399 at the C-terminal end of the large cytoplasmic loop of PS1. The latter residues contain a single arm-like domain and are highly conserved in the presenilins, suggesting that they form a functional armadillo **protein** binding site for the presenilins.

L26 ANSWER 24 OF 98 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1999151995 EMBASE [Contribution of molecular genetics in the clarification of
the cause and the role of current genetic research in the diagnosis of **Alzheimer** type dementia]. BIJDRAGE VAN DE MOLECULAIRE GENETICA IN DE ONTRAFELING VAN DE OORZAAK VAN ALZHEIMERDEMENTIE EN ROL VAN HET HUIDIG GENETISCH ONDERZOEK BIJ DE DIAGNOSESTELLING. Mortier G.R.. Dr. G.R. Mortier, Centrum Medische Genetica, Universitair Ziekenhuis, De Pintelaan 185, 9000 Gent, Belgium. Tijdschrift voor Geneeskunde 55/8 (573-577) 15 Apr 1999.
Refs: 48.
ISSN: 0371-683X. CODEN: TGEKBW. Pub. Country: Belgium. Language: Dutch.

L26 ANSWER 25 OF 98 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1999250231 EMBASE Isolation of human delta-catenin and its binding specificity with presenilin 1. Tanahashi H.; Tabira T.. H. Tanahashi, Div.
of Demyelinating Disease/Aging, National Institute of Neuroscience, 4-1-1 Ogawahigashi, Kodaira, Tokyo 187-8502, Japan. NeuroReport 10/3 (563-568) 25 Feb 1999.
Refs: 17.
ISSN: 0959-4965. CODEN: NERPEZ. Pub. Country: United Kingdom. Language: English. Summary Language: English.
AB We screened **proteins** for interaction with presenilin (PS) 1, and cloned the full-length cDNA of human delta-catenin, which encoded 1225 amino acids. Yeast two-hybrid assay, GST binding assay and immunoprecipitation demonstrated that delta-catenin interacted with a hydrophilic loop region in the endoproteolytic C-terminal fragment of PS1,
but not with that of PS-2. These results suggest that PS1 and PS2 partly differ in function. PS1 loop fragment containing the pathogenic mutation retained the binding ability. We also found another armadillo-**protein**, p0071, interacted with PS1.

L26 ANSWER 26 OF 98 MEDLINE
1999412497 Document Number: 99412497. Presenilins: molecular switches between proteolysis and signal transduction. Annaert W; De Strooper B. (Neuronal Cell Biology and Gene Transfer Laboratory, Centre for Human Genetics, Flanders Interuniversitary, Institute for Biotechnology (VIB4), Gasthuisberg, KULeuven, B-3000 Leuven, Belgium.) TRENDS IN NEUROSCIENCES,
(1999 Oct) 22 (10) 439-43. Ref: 63. Journal code: WEL. ISSN: 0166-2236. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Mis-sense mutations of presenilin 1 increase the release of amyloidogenic peptide from amyloid precursor **protein** (APP) and are a major cause of familial **Alzheimer**'s Disease. Loss-of-function mutations of presenilins in the mouse, Caenorhabditis elegans and Drosophila result in severe developmental defects caused by disturbed Notch signalling. Recent studies suggest that the diverse biological roles
of presenilin 1 can be explained at the molecular level by its role in the

proteolytic cleavage of the integral membrane domains of Notch and APP. This cleavage is a central switch in Notch signalling, while, for APP, its physiological role remains elusive. Evidence that presenilin 1 itself has catalytic properties could explain many of the biological and biochemical alterations caused by presenilin-1 deficiency or clinical mutations in presenilin 1. However, as presenilins reside in the endoplasmic reticulum and the cleavage of Notch and APP is believed to occur close to the cell membrane, the scientific field now faces a 'spatial paradox'.

L26 ANSWER 27 OF 98 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1999236825 EMBASE Presenilins, processing of .beta.-amyloid precursor **protein**, and Notch signaling. Chart Y.-M.; Yuh Nung Jan. Y.N. Jan, Howard Hughes Medical Institute, Department of Physiology, University of California, San Francisco, CA 94143-0725, United States. ynjan@itsa.ucsf.edu. Neuron 23/2 (201-204) 1999.
Refs: 22.
ISSN: 0896-6273. CODEN: NERNET. Pub. Country: United States. Language: English.

L26 ANSWER 28 OF 98 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1999191470 EMBASE C-terminal maturation fragments of presenilin 1 and 2 control secretion of APP.alpha. and A.beta. by human cells and are degraded by proteasome. Da Costa C.A.; Ancolio K.; Checler F.. F. Checler, Institut de Pharmacologie, Moleculaire/Cellulaire du CNRS, UPR 411, 660 Route des Lucioles, Sophia Antipolis, 06560 Valbonne, France. checler@ipmc.cnrs.fr. Molecular Medicine 5/3 (160-168) 1999.
Refs: 33.
ISSN: 1076-1551. CODEN: MOMEE2. Pub. Country: United States. Language: English. Summary Language: English.
AB Background: Most early-onset forms of **Alzheimer**'s disease are due to missense mutations located on two homologous **proteins** named presenilin 1 and 2 (PS 1 and PS2). Several lines of evidence indicate that PS 1 and PS2 undergo various post-transcriptional events including endoproteolytic cleavages, giving rise to 28-30 kD N-terminal (NTF) and 18-20 kD C-terminal (CTF) fragments that accumulate in vivo. Whether the biological activity of presenilins is borne by the processed fragments or their holoprotein precursor remains in question. We have examined the putative control of .beta.APP maturation by CTF-PS1/PS2 and the catabolic process of the latter **proteins** by the multicatalytic complex, proteasome. Materials and Methods: We transiently and stably transfected HEK293 cells with CTF-PS1 or CTF-PS2 cDNA. We examined these transfectants for their production of A.beta.40, A.beta.42, and APP.alpha. by immunoprecipitation using specific polyclonals. The effect of a series of proteases inhibitors on the immunoreactivity of CTF-PS1/PS2 was examined by Western blot. Finally, the influence of proteasome inhibitors on the generation of .beta.APP fragments by CTF-expressing cells was assessed by combined immunoprecipitation and densitometric analyses. Results: We showed that transient and stable transfection of CTF-PS1 and CTF-PS2 cDNAs in human cells leads to increased secretion of APP.alpha. and A.beta., the maturation products of .beta.APP. Furthermore, we demonstrated that two proteasome inhibitors, lactacystin and Z-IE(Ot-Bu)A-Leucinal, prevent the degradation of both CTFs. Accordingly, we established that proteasome inhibitors drastically potentiate the phenotypic increased production of APP.alpha. and A.beta. elicited by CTF-PS1/PS2. Conclusion: Our data establish that the C-terminal products

of PS 1 and PS2 maturation exhibit biological activity and in particular control .beta.APP maturation upstream to .alpha.-and .beta./.gamma.-secretase cleavages. This function is directly controlled by the proteasome that modulates the intracellular concentration of CTFs.

L26 ANSWER 29 OF 98 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1999238821 EMBASE Presenilin overexpression arrests cells in the G1 phase of the cell cycle: Arrest potentiated by the **Alzheimer**'s disease PS2(N141I) mutant. Janicki S.M.; Monteiro M.J.. Dr. M.J. Monteiro, Medical Biotechnology Center, 725 West Lombard Street, Baltimore, MD 21201, United States. monteiro@umbi.umd.edu. American Journal of Pathology 155/1 (135-144) 1999.
Refs: 43.
ISSN: 0002-9440. CODEN: AJPAA4. Pub. Country: United States. Language: English. Summary Language: English.
AB To investigate the mechanism by which presenilin (PS) overexpression induces apoptosis, we studied the effects of these **proteins** on cell cycle progression. Transiently transfected HeLa cells were bromodeoxyuridine (BrdU) labeled to visualize DNA synthesis by immunofluorescence and stained with propidium iodide to measure DNA content by fluorescence-activated cell sorting (FACS). BrdU labeling was decreased in cells expressing presenilin-1 (PS1), **presenilin-2** (PS2), an **Alzheimer**'s disease-associated missense mutation PS2(N141I), and the carboxyl-terminally deleted PS2 construct PS2(166aa), compared with mock and neurofilament-light (NF-L) transfected cells. Analysis of BrdU incorporation in mitotically synchronized HeLa cells suggested that cells were arresting in the G1 phase of the cell cycle, and this was confirmed by FACS analysis. Interestingly, cell cycle progression was more inhibited by the expression of PS2(N141I) compared with wild-type PS2. In addition, ATM, the gene product mutated in ataxia-telangiectasia, does not appear to be a downstream effector of PS-induced cell cycle arrest as transfection of PS constructs into an ataxia-telangiectasia cell line also resulted in cell cycle inhibition. Quantitative immunoblotting of whole-cell lysates from PS-transfected cells did not reveal increases or decreases in the steady-state levels of p21, p27, p53, pRb, or c-myc, suggesting that the presenilins mediate cell cycle arrest by mechanisms other than simple changes in the steady-state levels of these cell-cycle-related **proteins**.

L26 ANSWER 30 OF 98 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 10
1999:294766 Document No.: PREV199900294766. The amyloid precursor **protein** of **Alzheimer**'s disease and the Abeta peptide.
Storey, E. (1); Cappai, R.. (1) Van Cleef/Roet Centre for Nervous Diseases, Monash University, Commercial Road, Alfred Hospital Campus, Prahan, VIC, 3181 Australia. Neuropathology and Applied Neurobiology, (April, 1999) Vol. 25, No. 2, pp. 81-97. ISSN: 0305-1846. Language: English. Summary Language: English.
AB **Alzheimer**'s disease is characterized by the accumulation of beta amyloid peptides in plaques and vessel walls and by the intraneuronal accumulation of paired helical filaments composed of hyperphosphorylated tau. In this review, we concentrate on the biology of amyloid precursor **protein**, and on the central role of amyloid in the pathogenesis of **Alzheimer**'s disease. Amyloid precursor **protein** (APP) is part of a super-family of transmembrane and secreted **proteins**. It appears to have a number of roles, including regulation of haemostasis and mediation of neuroprotection. APP also has potentially important metal and heparin-binding properties, and the current challenge is to synthesize

all these varied activities into a coherent view of its function. Cleavage of amyloid precursor **protein** by beta-and gamma-secretases results in the generation of the Abeta (betaA4) peptide, whereas alpha-secretase cleaves within the Abeta **sequence** and prevents formation from APP. Recent findings indicate that the site ofgamma-secretase cleavage is critical to the development of amyloid deposits: Abeta1-42 is much more amyloidogenic than Abeta1-40. Abeta1-42 formation is favoured by mutations in the two presenilin genes (PS1 and PS2), and by the commonest amyloid precursor **protein** mutations. Transgenic mouse models of **Alzheimer**'s disease incorporating various mutations in the presenilin gene now exist, and have shown amyloid accumulation and cognitive impairment. Neurofibrillary tangles have not been reproduced in these models, however. While aggregated Abeta is neurotoxic, perhaps via an oxidative mechanism, the relationship between such toxicity and neurofibrillary tangle formation remains a subject of ongoing research.

L26 ANSWER 31 OF 98 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

1999251671 EMBASE Genetic variability at the amyloid-.beta. precursor **protein** locus may contribute to the risk of late-onset **Alzheimer**'s disease. Wavrant-De Vrieze F.; Crook R.; Holmans P.; Kehoe P.; Owen M.J.; Williams J.; Roehl K.; Laliiri D.K.; Shears S.; Booth J.; Wu W.; Goate A.; Chartier-Harlin M.C.; Hardy J.; Perez-Tur J.. J. Hardy, Mayo Clinic Jacksonville, 4500 San Pablo Road, Jacksonville, FL 32224, United States. hardy@mayo.edu. Neuroscience Letters 269/2 (67-70) 9 Jul 1999.

Refs: 28.

ISSN: 0304-3940. CODEN: NELED5.

Publisher Ident.: S 0304-3940(99)00417-6. Pub. Country: Ireland. Language:

English. Summary Language: English.

AB In a series of sibpairs with late onset **Alzheimer**'s disease, we have examined the segregation of the loci involved in the early onset, autosomal dominant form of the disorder by using flanking microsatellite repeat markers: thus we have used APP-PCR3 and D21S210 to examine the segregation of the amyloid-.beta. precursor **protein** (APP) gene, the markers DI 4S77 and D14S284 to examine the segregation of the presenilin 1 (PSI) gene and the markers D1S227, D1S249 and D1S419 to examine the segregation of **presenilin 2** (PS2). We carried out our analyses on the whole dataset of 291 affected sibpairs, and on subsets comprising those sibpairs in which neither had an apolipoprotein E4 allele (65 affected sibpairs) and those in which both had an apolipoprotein E4 allele (165 affected sibpairs). We used the programs SPLINK to generate allele frequencies and MAPMAKER/SIBS to analyze our results. We examined the segregation of the markers D19S908 and D19S918 that are close to the apolipoprotein E (ApoE) gene as a positive control to assess whether the methods we are employing have the capability to identify known loci. The sibpair approach to the identification of genetic risk loci is relatively insensitive as indicated by the failure of the ApoE locus to reach statistical significance (P = 0.06). Nevertheless, these data suggest that neither the PS1 nor the PS2 gene is a major locus for late-onset AD, but that the APP gene cannot be ruled out as a risk locus in those sibships without an E4 allele (P = 0.014). The possibility that APP is indeed a locus for late onset disease will need confirmation in other series of familial cases.

L26 ANSWER 32 OF 98 MEDLINE DUPLICATE 11

1999120637 Document Number: 99120637. A pedigree with a novel presenilin 1 mutation at a residue that is not conserved in **presenilin 2**. Yasuda M; Maeda K; Hashimoto M; Yamashita H; Ikejiri Y; Bird T D; Tanaka C; Schellenberg G D. (Hyogo Institute for Aging Brain and Cognitive Disorders, Himeji, Japan.. yasuda@hiabcd.go.jp) . ARCHIVES OF NEUROLOGY, (1999 Jan) 56 (1) 65-9. Journal code: 80K. ISSN: 0003-9942. Pub. country: United States. Language: English.

AB OBJECTIVE: To disclose a novel mutation of the presenilin 1 (PS1) gene responsible for early-onset **Alzheimer** disease and to clarify genotype-phenotype correlation that should help to establish the function of this **protein**. BACKGROUND: The PS1 and **presenilin 2** (PS2) genes carry missense mutations in families with **Alzheimer** disease. The PS1 and PS2 **proteins** have similar structures, and all presently known mutations are in nucleotides coding for amino acids that are conserved between the 2 presenilins. METHODS: **Sequence** and restriction fragment length polymorphism analyses of PS1 gene of DNA from a pedigree with early-onset **Alzheimer** disease. RESULTS: **Sequence** analysis disclosed a novel PS1 mutation in a pedigree of Japanese origin with early-onset **Alzheimer** disease. This mutation, which is predicted to cause a missense substitution of lysine for glutamic acid, occurred at codon 123 of PS1 that was not a conserved residue in PS2. The 2 patients of this pedigree shared an early clinical phenotype consisting of later-onset, progressive aphasia, but preserved visuospatial ability, which was indistinguishable from those of other PS1-associated **Alzheimer** disease cases. CONCLUSION: These results demonstrate that a missense mutation in a region not conserved between PS1 and PS2 can cause **Alzheimer** disease.

L26 ANSWER 33 OF 98 MEDLINE DUPLICATE 12

1999176858 Document Number: 99176858. Mapping the APP/presenilin (PS) binding domains: the hydrophilic N-terminus of PS2 is sufficient for interaction with APP and can displace APP/PS1 interaction. Pradier L; Carpentier N; Delalonde L; Clavel N; Bock M D; Buee L; Mercken L; Tocque B; Czech C. (Gene Medicine Department, Rhone-Poulenc Rorer, Vitry, France.. laurent.pradier@rp-rorer.fr) . NEUROBIOLOGY OF DISEASE, (1999 Feb) 6 (1) 43-55. Journal code: CUN. ISSN: 0969-9961. Pub. country: United States. Language: English.

AB Mutations in presenilin 1 and **presenilin 2** (PS1 and PS2, respectively) genes cause the large majority of familial forms of early-onset **Alzheimer**'s disease. The physical interaction between presenilins and APP has been recently described using coimmunoprecipitation. With a similar technique, we confirmed this interaction and have mapped the interaction domains on both PS2 and APP. Using several carboxy-terminal truncated forms of PS2, we demonstrated that the hydrophilic amino terminus of PS2 (residues 1 to 87, PS2NT) was sufficient for interaction with APP. Interestingly, only a construct with a leader peptide for secretion (SecPS2NT) and not its cytosolic counterpart was shown to interact with APP. For APP, we could demonstrate interaction of PS2 with the last 100 but not the last 45 amino acids of APP, including therefore the A beta region. Accordingly, SecPS2NT is capable of binding to A beta-immunoreactive species in conditioned medium.

In addition, a second region in the extracellular domain of APP also interacted with PS2. Comparable results with PS1 indicate that the two presenilins share similar determinants of binding to APP. Confirming these results, SecPS2NT is able to inhibit PS1/APP interaction. Such a competition makes it unlikely that the PS/APP interaction results from nonspecific aggregation of PS in transfected cells. The physical interaction of presenilins with a region encompassing the A beta

sequence of APP could be causally related to the misprocessing of APP and the production of A beta1-42.

L26 ANSWER 34 OF 98 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1999082010 EMBASE Effects of presenilin N-terminal fragments on production of
amyloid .beta. peptide and accumulation of endogenous presenilins.
Shirotani K.; Takahashi K.; Tabira T.. K. Shirotani, Div. of Demyelinating
Dis. and Aging, National Institute of Neuroscience, NCNP, 4-1-1 Ogawahigashi, Kodaira, Tokyo 187-8502, Japan. Neuroscience Letters 262/1 (37-40) 26 Feb 1999.
Refs: 20.
ISSN: 0304-3940. CODEN: NELED5.
Publisher Ident.: S 0304-3940(99)00037-3. Pub. Country: Ireland. Language:
English. Summary Language: English.
AB To clarify the effects of the proteolytic cleavage of presenilin 1 (PS1) and **presenilin 2** (PS2) **proteins** on their functions, we established stable cell lines which expressed the physiologically cleaved N-terminal fragment (NTF) with or without mutations of familial **Alzheimer**'s disease (FAD). We found that exogenous expression of the PS1-NTF or PS2-NTF harboring FAD mutations was
insufficient for increased production of amyloidogenic A.beta. X- 42 peptide and that the overexpressed NTFs had no effect on the accumulation of endogenous presenilin fragments.

L26 ANSWER 35 OF 98 MEDLINE
1999319748 Document Number: 99319748. Translating cell biology into therapeutic advances in **Alzheimer**'s disease. Selkoe D J. (Center for Neurologic Diseases, Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts 02115, USA.) NATURE, (1999 Jun 24) 399 (6738 Suppl) A23-31. Ref: 100. Journal code: NSC. ISSN: 0028-0836. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Studies of the molecular basis of **Alzheimer**'s disease exemplify the increasingly blurred distinction between basic and applied biomedical research. The four genes so far implicated in familial **Alzheimer**'s disease have each been shown to elevate brain levels of the self-aggregating amyloid-beta **protein**, leading gradually to profound neuronal and glial alteration, synaptic loss and dementia. Progress in understanding this cascade has helped to identify specific therapeutic targets and provides a model for elucidating other neurodegenerative disorders.

L26 ANSWER 36 OF 98 CAPLUS COPYRIGHT 2000 ACS
1998:709095 Document No. 129:327534 A purified 20 kda **presenilin 2** C-terminal fragment and methods of screening for compounds that inhibit proteolysis of **presenilin 2**. Tanzi, Rudolph E.; Kim, Tae-Wan (USA). PCT Int. Appl. WO 9847917 A2 19981029, 83 pp.
DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2.
APPLICATION: WO 1998-US8260 19980424. PRIORITY: US 1997-44262 19970424.
AB The present invention relates, in general, to **presenilin 2** proteolytic fragments. In particular, the present invention relates to a purified 20 kDa **presenilin 2** C-terminal fragment (PS2-CTF); purified nucleic acid mols. coding for the 20 kDa PS2-CTF **protein**; cells contg. the nucleic acid mols.; non-human organisms contg. the nucleic acid mol.; antibodies having specific binding

affinity to the 20 kDa PS2-CTF; hybridomas contg. the antibodies; methods of detecting 20 kDa PS2-CTF in a sample; diagnostic kits; methods for screening compds. that inhibit proteolytic processing of **presenilin 2** in a cell, isolated compds. that inhibit proteolytic processing of **presenilin 2** in a cell, and a method of inhibiting apoptotic cell death by preventing proteolytic cleavage of **presenilin 2** at a cleavage site which generates a 20 kDa C-terminal fragment. Thus, using a stably transfected, inducible cell system, it was found that PS2 is proteolytically cleaved into two stable cellular **protein** including an .apprx.20 kDa C-terminal fragment and an .apprx.34 kDa N-terminal fragment. PS2 is polyubiquitinated in vivo and the degrdn. of PS2 is inhibited by proteasome inhibitors, N-acetyl-L-leucinal-L-norleucinal and lactacystin. Both PS1 and PS2 wer alternatively cleaved at sites distal to their normal cleavage sites when apoptosis was induced in untransfected H4 human neuroglioma cells or when these genes were overexpressed. Alternative cleavage of PS1 and PS2 could be blocked by treatment with either sVAD (a broad spectrum caspase inhibitor) or zDEVD (a CPP32-like protease inhibitor) indicating that the enzyme responsible is a CPP32-like protease. In H4 cells overexpressing PS2 contg. the N141I familial **Alzheimer**'s disease (FAD) mutation, the ration of apoptotic:normal cleavage fragments was significantly elevated compared to wild-type PS2-expressing cells. Thus, apoptosis-assocd. endoproteolysis of the presenilins mediated by a CPP32-like protease plays a role in the pathogenesis of FAD.

L26 ANSWER 37 OF 98 MEDLINE DUPLICATE 13

1998361992 Document Number: 98361992. Molecular dissection of domains in mutant **presenilin 2** that mediate overproduction of amyloidogenic forms of amyloid beta peptides. Inability of truncated forms of PS2 with familial **Alzheimer**'s disease mutation to increase secretion of Abeta42. Tomita T; Tokuhiro S; Hashimoto T; Aiba K; Saido T C; Maruyama K; Iwatsubo T. (Department of Neuropathology and Neuroscience, Graduate School of Pharmaceutical Sciences, University of Tokyo, Tokyo 113-0033, Japan.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Aug 14) 273 (33) 21153-60. Journal code: HIV. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Mutations in presenilin (PS) 1 or PS2 genes account for the majority of early-onset familial **Alzheimer**'s disease, and these mutations have been shown to increase production of species of amyloid beta peptide (Abeta) ending at residue 42, i.e. the most amyloidogenic form of Abeta. To gain insight into the molecular mechanisms whereby mutant PS induces overproduction of Abeta42, we constructed cDNAs encoding mutant and/or truncated forms of PS2 and examined the secretion of Abeta42 from COS or neuro2a cells transfected with these genes. Cells expressing full-length PS2 harboring both N141I and M239V mutations in the same polypeptide induced overproduction of Abeta42, although the levels of Abeta42 were comparable with those in cells engineered to express PS2 with one or the other of these PS2 mutations. In contrast, cells engineered to express partially truncated PS2 (eliminating the COOH-terminal third of PS2 while retaining the endoproteolytic NH2-terminal fragment) and harboring a N141I mutation, as well as cells expressing COOH-terminal fragments of PS2, did not overproduce Abeta42, and the levels of Abeta42 were comparable with those in cells that expressed full-length, wild-type PS2 or fragments thereof. These data indicate that: (i) the Abeta42-promoting effects of

mutant PS2 **proteins** reach the maximum level with a given single amino acid substitution (i.e. N141I or M239V); and (ii) the expression of full-length mutant PS2 is required for the overproduction of Abeta42. Hence, cooperative interactions of NH2- and COOH-terminal fragments generated from full-length mutant PS2 may be important for the overproduction of Abeta42 that may underlie familial **Alzheimer**'s disease.

L26 ANSWER 38 OF 98 MEDLINE DUPLICATE 14
1998226633 Document Number: 98226633. Proteolytic fragments of the **Alzheimer**'s disease associated presenilins-1 and -2 are phosphorylated in vivo by distinct cellular mechanisms. Walter J; Grunberg J; Schindzielorz A; Haass C. (Department of Molecular Biology, Central Institute of Mental Health, Mannheim, Germany.) BIOCHEMISTRY, (1998 Apr 28) 37 (17) 5961-7. Journal code: A0G. ISSN: 0006-2960. Pub. country: United States. Language: English.

AB The majority of familial **Alzheimer**'s disease mutations are linked to the recently cloned presenilin (PS) genes, which encode two highly homologous **proteins** (PS-1 and PS-2). Full-length PS **proteins** undergo endoproteolytic cleavage within their hydrophilic loop domain resulting in the formation of C-terminal (CTF) and N-terminal fragments (NTF). PS-2 was found to be phosphorylated as a full-length **protein** within its N-terminal domain. In contrast, PS-1 is phosphorylated selectively after proteolytic processing within its approximately 20 kDa CTF involving **protein** kinase C (PKC) and/or **protein** kinase A (PKA). We now have found that the CTF of the highly homologous PS-2 is also phosphorylated. Surprisingly, the PS-2 CTF is not phosphorylated by PKC or PKA. Instead, the PS-2 CTF is constitutively phosphorylated in vivo by serine/threonine **protein** kinases, which are independent of phorbol ester and intracellular cAMP. In vitro the large hydrophilic loop of PS-2 between transmembrane domains 6 and 7 can be phosphorylated by casein kinase-1 (CK-1) and CK-2, but not by PKA or PKC. Quantitative analysis of in vitro phosphorylation demonstrates the presence of two phosphorylation sites for CK-1 and a single site for CK-2. A deletion analysis revealed that the CTF of PS-2 is phosphorylated in vivo within an acidic **sequence** containing three potential phosphorylation sites for CKs (serines 327, 330, and 335). These data suggest that CK type **protein** kinases phosphorylate the CTF of PS-2 within its hydrophilic loop domain in vivo. Interestingly, the potential phosphorylation sites are located directly adjacent to the recently identified caspase cleavage sites.

L26 ANSWER 39 OF 98 BIOSIS COPYRIGHT 2000 BIOSIS DUPLICATE 15
1999:28142 Document No.: PREV199900028142. Truncated **presenilin 2** derived from differentially spliced mRNAs does not affect the ratio of amyloid beta-peptide 1-42/1-40. Gruenberg, Juergen; Walter, Jochen; Eckman, Chris; Capell, Anja; Schindzielorz, Alice; Younkin, Steven; Mehta, Nitin; Hardy, John; Haass, Christian (1). (1) Central Inst. Mental Health, Dep. Molecular Biol., J5, 68159 Mannheim Germany. Neuroreport, (Oct. 5, 1998) Vol. 9, No. 14, pp. 3293-3299. ISSN: 0959-4965. Language: English.

AB Numerous mutations in the presenilin (PS) genes cause early onset familial **Alzheimer**'s disease (FAD). Here we characterize the expression of two naturally occurring alternative PS2 transcripts which lack either exons 3 and 4 (PS2 DELTAexon3,4) or exons 3, 4, and 8 (PS2

DELTAexon3,4,8). These transcripts do not contain the natural initiation codon within exon 3. The transcripts are efficiently translated as N-terminal truncated **proteins**. These deleted **proteins** are still able to regulate formation of endogenous PS fragments, indicating that the C-terminal half of the PS2-**protein** is sufficient for this phenomenon. Although apprx50% of the PS1 and both PS2 mutations occur within the N-terminal region lacking in the PS2 DELTAexon3,4 and PS2 DELTAexon3,4,8 **proteins**, expression of these truncated **proteins** does not affect pathological generation of amyloid beta-peptide (Abeta). This suggests that point mutations causing AD are gain of function mutations.

L26 ANSWER 40 OF 98 MEDLINE DUPLICATE 16
1998442695 Document Number: 98442695. Calsenilin: a calcium-binding **protein** that interacts with the presenilins and regulates the levels of a presenilin fragment [see comments]. Buxbaum J D; Choi E K; Luo Y; Lilliehook C; Crowley A C; Merriam D E; Wasco W. (Department of Psychiatry, Mount Sinai School of Medicine, New York, New York 10029, USA.. buxbaj01@doc.mssm.edu) . NATURE MEDICINE, (1998 Oct) 4 (10) 1177-81.
Journal code: CG5. ISSN: 1078-8956. Pub. country: United States. Language: English.
AB Most early-onset familial **Alzheimer** disease (AD) cases are caused by mutations in the highly related genes presenilin 1 (PS1) and **presenilin 2** (PS2). Presenilin mutations produce increases in beta-amyloid (Abeta) formation and apoptosis in many experimental systems. A cDNA (ALG-3) encoding the last 103 amino acids of PS2 has been identified as a potent inhibitor of apoptosis. Using this PS2 domain in the yeast two-hybrid system, we have identified a neuronal **protein** that binds calcium and presenilin, which we call calsenilin. Calsenilin interacts with both PS1 and PS2 in cultured cells, and can regulate the levels of a proteolytic product of PS2. Thus, calsenilin may mediate the effects of wild-type and mutant presenilins on apoptosis and on Abeta formation. Further characterization of calsenilin may lead to an understanding of the normal role of the presenilins and of the role of the presenilins in **Alzheimer** disease.

L26 ANSWER 41 OF 98 MEDLINE DUPLICATE 17
1998099802 Document Number: 98099802. Interaction of presenilins with the filamin family of actin-binding **proteins**. Zhang W; Han S W; McKeel D W; Goate A; Wu J Y. (Department of Pediatrics and Molecular Biology and Pharmacology, Washington University School of Medicine, St. Louis, Missouri 63110, USA.) JOURNAL OF NEUROSCIENCE, (1998 Feb 1) 18 (3) 914-22. Journal code: JDF. ISSN: 0270-6474. Pub. country: United States. Language: English.
AB Mutations in presenilin genes PS1 and PS2 account for approximately 50% of early-onset familial **Alzheimer**'s disease (FAD). The PS1 and PS2 genes encode highly homologous transmembrane **proteins** related to the Caenorhabditis elegans sel-12 and spe-4 gene products. A hydrophilic loop region facing the cytoplasmic compartment is likely to be functionally important because at least 14 mutations in FAD patients have been identified in this region. We report here that the loop regions of PS1 and PS2 interact with nonmuscle filamin (actin-binding **protein** 280, ABP280) and a structurally related **protein** (filamin homolog 1, Fh1). Overexpression of PS1 appears to modify the distribution of ABP280 and Fh1 **proteins** in cultured cells. A monoclonal antibody

recognizing ABP280 and Fh1 binds to blood vessels, astrocytes, neurofibrillary tangles, neuropil threads, and dystrophic neurites in the AD brain. Detection of ABP280/Fh1 **proteins** in these structures suggests that these presenilin-interacting **proteins** may be involved in the development of AD and that interactions between presenilins and ABP280/Fh1 may be functionally significant. The ABP280 gene is located on the human X chromosome, whereas the newly identified Fh1 gene maps to human chromosome 3. These results provide a new basis for understanding the function of presenilin **proteins** and further implicate cytoskeletal elements in AD pathogenesis.

L26 ANSWER 42 OF 98 MEDLINE DUPLICATE 18
1998439039 Document Number: 98439039. Presenilins--in search of functionality. Karran E H; Allsop D; Christie G; Davis J; Gray C; Mansfield F; Ward R V. (Neurosciences Research, SmithKline Beecham Pharmaceuticals, New Frontiers Science Park, Harlow, Essex, UK.)
BIOCHEMICAL SOCIETY TRANSACTIONS, (1998 Aug) 26 (3) 491-6. Ref: 48.
Journal code: E48. ISSN: 0300-5127. Pub. country: ENGLAND: United Kingdom.
Language: English.
AB The discovery of the PS **proteins**, the complexities of their biochemistry and their potential involvement in signalling pathways and in apoptosis have galvanized research into AD. To date, the aspect of the functionality of the PSs most relevant to the pathology of AD is the effect of PS FAD mutants to increase the proportion of A beta 42 produced from cells. This, coupled to the observation that gamma-secretase cleavage is considerably reduced in neurons derived from PS-1 knockout mice, argues strongly that PS plays a very direct role in the proteolytic processing of APP.

L26 ANSWER 43 OF 98 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1998147099 EMBASE Stable association of presenilin derivatives and absence of presenilin interactions with APP. Thinakaran G.; Regard J.B.; Bouton C.M.L.; Harris C.L.; Price D.L.; Borchelt D.R.; Sisodia S.S.. G. Thinakaran, Department of Pathology, Johns Hopkins Univ. School of Med., Baltimore, MD 21205-2196, United States. Neurobiology of Disease 4/6 (438-453) 1998.
Refs: 62.
ISSN: 0969-9961. CODEN: NUDIEM. Pub. Country: United States. Language: English. Summary Language: English.
AB Mutations in two related genes, presenilin 1 and **presenilin 2** (PS1 and PS2), cosegregate with **Alzheimer**'s disease. PS1 and PS2 are highly homologous polytopic membrane **proteins** that are subject to endoproteolytic cleavage in vivo. The resulting N- and C-terminal derivatives are the preponderant PS- related species that accumulate in cultured cells and tissue. In earlier studies, we demonstrated that PS1 N- and C-terminal derivatives accumulate to 1:1 stoichiometry and that the absolute levels of fragments are established by a tightly regulated and saturable mechanism. These findings led to the suggestion that the levels of PS1 derivatives might be determined by their association with limiting cellular components. In this study, we use in situ chemical cross-linking and coimmunoprecipitation analyses to document

that the N- and C-terminal derivatives of either PS1 or PS2 can be coisolated. Moreover, and in contrast to published reports which documented that PS1 and PS2 form stable heteromeric assemblies with the .beta.-amyloid precursor **protein** (APP), we have failed to provide evidence for physiological complexes between PS1 and PS2 holoproteins or their derivatives with APP.

L26 ANSWER 44 OF 98 MEDLINE DUPLICATE 19
1999167105 Document Number: 99167105. Cloning of the **presenilin 2** cDNA and its distribution in brain of the primate, Microcebus murinus: coexpression with betaAPP and Tau **proteins**. Calenda A; Mestre-Frances N; Czech C; Pradier L; Petter A; Perret M; Bons N; Bellis M. (CNRS ERS 155, Institut de Biologie, Montpellier, France.) NEUROBIOLOGY OF DISEASE, (1998 Nov) 5 (5) 323-33. Journal code: CUN. ISSN: 0969-9961. Pub. country: United States. Language: English.
AB A 1340-bp cDNA fragment encoding the lemurian **presenilin 2 protein** (PS2) was isolated from a Microcebus murinus brain cDNA library by PCR using oligonucleotide primers based on the nucleotide **sequence** of the human gene. Analysis of five isolated clones showed that the **sequence** encoded a 448-amino-acid open reading frame, 95.5% identical to the human and 93.5% identical to the mouse **presenilin 2 sequences**. However, neither the localization of the 2 positions in PS2 nor that of the 43 positions in PS1 associated with early onset **Alzheimer**'s disease were changed. Expression of the **presenilin 2** was detected by RT-PCR and compared with that of presenilin 1 and betaAPP in the brain and in peripheral tissues (liver, kidney, and spleen). Immunohistochemistry with a specific polyclonal antiserum raised against a synthetic peptide from the N-terminal part of the human PS2 showed that the **protein** is distributed throughout the microcebe brain, in vascular and nerve structures. In cortical and in subcortical areas, PS2 labeling was weak and granular in appearance and was scattered throughout the cytoplasm of many neurones, extending into neurites. The gene expression of PS2 increased with age but was not affected by the presence of numerous amyloid plaques. Double labeling immunocytochemistry detected very few neurones with combined immunoreactivity PS2 and APP, or PS2 and Tau.

L26 ANSWER 45 OF 98 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
1998212122 EMBASE Mutant **presenilin 2** transgenic mouse: Effect on an age-dependent increase of amyloid .beta.-**protein** 42 in the brain. Oyama F.; Sawamura N.; Kobayashi K.; Morishima-Kawashima M.; Kuramochi T.; Ito M.; Tomita T.; Maruyama K.; Saido T.C.; Iwatsubo T.; Capell A.; Walter J.; Grunberg J.; Ueyama Y.; Haass C.; Ihara Y.. Dr. Y. Ihara, Department of Neuropathology, Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113, Japan. Journal of Neurochemistry 71/1 (313-322) 1998.
Refs: 37.
ISSN: 0022-3042. CODEN: JONRA. Pub. Country: United States. Language: English. Summary Language: English.
AB The N1411 missense mutation in presenilin (PS) 2 is tightly linked with a form of autosomal dominant familial **Alzheimer**'s disease (AD) in the Volga German families. We have generated transgenic mouse lines overexpressing human wild-type or mutant PS2 under transcriptional control of the chicken .beta.-actin promoter. In the brains of transgenic mice, the levels of human PS2 mRNA were found to be five- to 15-fold higher than

that of endogenous mouse PS2 mRNA. The amyloid .beta.-**protein** (A.beta.) 42 levels in the brains of mutant PS2 transgenic mice were higher than those in wild-type PS2 transgenic mice at the age of 2, 5, or 8 months. In addition, the A.beta.42 levels appeared to increase steadily in the mutant PS2 transgenic mouse brains from 2 to 8 months of age, whereas there was only a small increase in wild-type transgenic mice between the ages of 5 and 8 months. There was no definite difference in the levels of N-terminal and C-terminal fragments between wild- type and mutant PS2 transgenic mice at the age of 2, 5, or 8 months. These data show a definite effect of the PS2 mutation on an age-dependent increase of A.beta.42 content in the brain.

L26 ANSWER 46 OF 98 MEDLINE DUPLICATE 20

1998207716 Document Number: 98207716. Cloning of the cDNA encoding rat **presenilin-2**. Tanahashi H; Tabira T. (Division of Demyelinating Disease and Aging, National Institute of Neuroscience, Tokyo, Japan.. tanahashi@ncnpja.ncnp.go.jp) . BIOCHIMICA ET BIOPHYSICA ACTA, (1998 Mar 13) 1396 (3) 259-62. Journal code: A0W. ISSN: 0006-3002. Pub. country: Netherlands. Language: English.

AB We report here the cDNA **sequence** of rat homologue of **presenilin-2** (PS-2). The rat PS-2 cDNA encoded 448 amino acids, and the deduced amino acid **sequence** was highly homologous to those of the human (94.9%), mouse (96.4%) and Xenopus (70.8%). A minor splicing variant lacking a single glutamate was detected, while the product corresponding to the exon 9 deleted splicing variant observed in human was not detected.

L26 ANSWER 47 OF 98 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

1998095884 EMBASE Presenilin mutations in **Alzheimer**'s disease. Cruts M.; Van Broeckhoven C.. Dr. C. Van Broeckhoven, Laboratory of Neurogenetics, Department of Biochemistry, University of Antwerp (U1A), Universiteitsplein 1, B-2018 Antwerpen, Belgium. cvbroeck@uia.ac.be.

Human Mutation 11/3 (183-190) 1998.
Refs: 64.
ISSN: 1059-7794. CODEN: HUMUE3. Pub. Country: United States. Language: English. Summary Language: English.

AB The presenilins (PS-1 and PS-2) are 2 members of a novel family of genes encoding integral membrane **proteins** recently implicated in **Alzheimer**'s disease (AD) pathology. To date, 43 mutations have been identified in PS-1 and 2 in PS-2 that lead to familial presenile AD (onset before age 65 years). The normal and pathological functions of the PS **proteins** (ps-1 and ps-2) are unknown, but their high degree of homology predicts similar biological activities. Homologies with ps from other species suggest that they may play a role in intracellular **protein** sorting and trafficking, in intercellular cell signaling, or in cell death. Since to date only missense mutations and in-frame deletions were identified, it is believed that mutated ps act through either a gain of (dys-) function or a dominant negative effect. In vivo and in vitro studies have linked PS mutations to amyloid deposition, an early pathological event in AD brains.

L26 ANSWER 48 OF 98 MEDLINE

1998366011 Document Number: 98366011. Proteolytic processing of **Alzheimer**'s disease associated **proteins**. Haass C; Grunberg J; Capell A; Wild-Bode C; Leimer U; Walter J; Yamazaki T; Ihara I; Zweckbronner I; Jakubek C; Baumeister R. (Central Institute for Mental Health, Department of Molecular Biology, Mannheim, Federal Republic of Germany.) JOURNAL OF NEURAL TRANSMISSION. SUPPLEMENTUM, (1998) 53 159-67.

Ref: 39. Journal code: JAK. ISSN: 0303-6995. Pub. country: Austria. Language: English.

AB Amyloid beta-peptide (A beta), the major component of senile plaques, is generated by proteolytic processing from the beta-amyloid precursor **protein** (beta APP). Mutations within the beta APP gene cause early onset familial AD (FAD) by affecting A beta generation. Interestingly, the much more abundant mutations within the presenilin (PS) genes also result in the abnormal generation of a 42 residue A beta (A beta 42), thus clearly supporting a pivotal role of A beta for the pathology of AD. PS **proteins** are proteolytically processed into stable 30 kDa N-terminal fragments (NTF) and 20 kDa C-terminal fragments (CTF). Beside the conventional proteolytic pathway. PS **proteins** can also be cleaved further C-terminal by proteases of the caspase superfamily. PS **proteins** were localized within the endoplasmic reticulum (ER) and early Golgi, compartments which we have demonstrated to be involved in A beta 42 generation and intracellular accumulation. Using Caenorhabditis elegans as a simple animal model, we demonstrate that PS **proteins** are involved in NOTCH signaling FAD causing mutations interfere with the biological function of PS **proteins** in NOTCH signaling.

L26 ANSWER 49 OF 98 CAPLUS COPYRIGHT 2000 ACS

1998:695608 Document No. 130:91785 Identification of peptides binding to presenilin 1 by screening of random peptide display libraries. Schwarzman, Alexander; Tsiper, Maria; Vitek, Michael; **St. George-Hyslop, Peter**; Goldgaber, Dmitry (Department of Psychiatry, SUNY, Stony Brook, NY, USA). Adv. Behav. Biol., 49(Progress in Alzheimer's and Parkinson's Diseases), 141-147 (English) 1998. CODEN: ADBBBW. ISSN: 0099-6246. Publisher: Plenum Publishing Corp..

AB In order to identify presenilin 1 (PS-1) and **presenilin 2** (PS-2) binding peptides and **proteins**, the authors screened random peptide display libraries using recombinant PS-1 as a binding target.

L26 ANSWER 50 OF 98 MEDLINE

1999418070 Document Number: 99418070. Genetics of **Alzheimer**'s disease. Hutton M; Perez-Tur J; Hardy J. (Neurogenetics Laboratory, Mayo Clinic Jacksonville, FL 32224, USA.) ESSAYS IN BIOCHEMISTRY, (1998) 33 117-31. Ref: 65. Journal code: EMG. ISSN: 0071-1365. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Mutations in any one of three genes can cause autosomal dominant, early-onset **Alzheimer**'s disease: these genes are the amyloid precursor **protein** (APP) gene on chromosome 21, the presenilin-1 (PS-1) gene on chromosome 14 and the **presenilin-2** (PS-2) gene on chromosome 1. Pathogenic mutations at all these loci cause mismetabolism of APP such that more of the peptide A beta 42 is produced. This peptide is deposited in the plaques in the brains of **Alzheimer**'s patients. These facts have led to the dominant hypothesis for the disease process: the 'amyloid cascade hypothesis', which proposes that overproduction or failure to clear the peptide A beta 42 is always central to the disease. Genetic variability at the apoliprotein E locus is a major determinant of late onset **Alzheimer**'s disease. The mechanism by which apoliprotein E is involved in the pathogenesis of **Alzheimer**'s disease is not yet known. There are likely to be other genetic factors which impinge on **Alzheimer**'s disease.

L26 ANSWER 51 OF 98 MEDLINE

1998227381 Document Number: 98227381. [Presenilins: detection and characterization of **Alzheimer**'s disease genes]. Preseniliny: obnaruzhenie i kharakteristika genov bolezni Al'tsgeimera. Rogaev E I.

MOLEKULIARNAIA BIOLOGIIA, (1998 Jan-Feb) 32 (1) 71-83. Ref: 41. Journal code: NGX. ISSN: 0026-8984. Pub. country: RUSSIA: Russian Federation. Language: Russian.

L26 ANSWER 52 OF 98 MEDLINE

1998267265 Document Number: 98267265. Cloning and characterization of the **presenilin-2** gene promoter. Pennypacker K R; Fuldner R; Xu R; Hernandez H; Dawbarn D; Mehta N; Perez-Tur J; Baker M; Hutton M. (Department of Pharmacology and Therapeutics, University of South Florida, Tampa, FL 33612, USA.) BRAIN RESEARCH. MOLECULAR BRAIN RESEARCH, (1998 May) 56 (1-2) 57-65. Journal code: MBR. ISSN: 0169-328X. Pub. country: Netherlands. Language: English.

AB Mutations in the **presenilin-2** (PS-2) have been shown to cause early onset **Alzheimer**'s disease (AD) in a series of families known as the Volga Germans and in an unrelated Italian kindred. Expression of the PS-2 gene is regulated during AD, aging, development and brain injury. Although expressed primarily in neurons, enhanced levels of PS-2 have been reported in astrocytes activated by neuronal damage. Understanding the regulation of the PS-2 gene may thus provide an insight into its role in AD. We have isolated a 3635 bp DNA fragment that contains 2934 bp of DNA **sequence** upstream from the PS-2 gene. Primer extension analysis was used to map three major transcriptional start sites within the PS-2 gene. The promoter **sequence**, upstream of each transcriptional start site, does not contain TATA or CAAT boxes but does contain several GC rich sites (Sp-1 and AP-2). A reporter gene construct containing the PS-2 promoter (PS2P, -2934 to +702) transfected into M17 cells drives basal transcription to 20% of the levels of the SV-40 viral promoter. Addition of NGF to PC-12 cells was found to upregulate the PS2P promoter and an NGF-responsive element was localized by deletional analysis between -403 and +13 within the promoter. Since the PS-2 gene has multiple start sites and the upstream **sequence** is GC rich with no TATA box, the PS-2 promoter is consistent with the GC class of 'housekeeping' genes. Copyright 1998 Elsevier Science B.V.

L26 ANSWER 53 OF 98 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

1998170947 EMBASE Short communication: Somatic mutation analysis of the APP and pesenilin 1 and 2 genes in **Alzheimer**'s disease brains. Reznik-Wolf H.; Machado J.; Haroutunian V.; DeMarco L.; Walter G.F.; Goldman B.; Davidson M.; Johnston J.A.; Lannfelt L.; Dani S.U.; Friedman E.. E. Friedman, Institute of Genetics, Chaim Sheba Medical Center, Tel-Hashomer, Israel. feitan@post.tau.ac.il. Journal of Neurogenetics 12/1 (55-65) 1998.
Refs: 27.
ISSN: 0167-7063. CODEN: JLNEDK. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB The molecular basis for sporadic **Alzheimer** disease (AD) remains largely unknown. We hypothesized that in some cases of sporadic AD, a somatic mutation in an embryonic cell committed to neuronal development within the amyloid precursor **protein** (APP), the presenilin 1 (PS-1) or the **presenilin 2** (PS-2) genes (genes known to be involved in familial AD) may result in AD phenotype. Using PCR, denaturing gradient gel electrophoresis (DGGE), restriction enzyme digest and direct DNA sequencing, we analyzed these genes in 99 brain tissues from patients with histopathologically proven AD. One brain sample showed a mutation within the PS-1 gene, His163 Arg, later shown to be a germline mutation. No other migration abnormalities were demonstrated in any sample

in exon 16 or 17 of the APP gene or the coding exons of the PS- 1 gene. Restriction digest pattern was normal with regard to the predominant PS-2 gene mutation (N141I). A known mutation in the APP gene, as well as novel mutations within the PS-1 gene were easily detected by DGGE (Reznick Wolf et al. manuscript submitted). We conclude that the genes that are involved in familial AD do not display somatic mutations in the brains of sporadic AD patients, and that other molecular mechanisms are probably involved in the pathogenesis of sporadic AD.

L26 ANSWER 54 OF 98 MEDLINE DUPLICATE 21
1998046005 Document Number: 98046005. Estimation of the genetic contribution of presenilin-1 and -2 mutations in a population-based study of presenile **Alzheimer** disease. Cruts M; van Duijn C M; Backhovens H; Van den Broeck M; Wehnert A; Serneels S; Sherrington R; Hutton M; Hardy J; **St George-Hyslop P H**; Hofman A; Van Broeckhoven C. (Laboratory of Neurogenetics, Flanders Interuniversity Institute for Biotechnology (VIB), Born-Bunge Foundation (BBS), University of Antwerp (UIA), Department of Biochemistry, Antwerpen, Belgium.) HUMAN MOLECULAR GENETICS, (1998 Jan) 7 (1) 43-51. Journal code: BRC. ISSN: 0964-6906. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Two closely related genes, the presenilins (PS), located at chromosomes 14q24.3 and 1q42.1, have been identified for autosomal dominant **Alzheimer** disease (AD) with onset age below 65 years (presenile AD). We performed a systematic mutation analysis of all coding and 5'-non-coding exons of PS -1 and PS -2 in a population-based epidemiological series of 101 unrelated familial and sporadic presenile AD cases. The familial cases included 10 patients of autosomal dominant AD families sampled for linkage analysis studies. In all patients mutations in the amyloid precursor **protein** gene (APP) had previously been excluded. Four different PS -1 missense mutations were identified in six familial cases, two of which where autosomal dominant cases. Three mutations resulted in onset ages above 55 years, with one segregating in an autosomal dominant family with mean onset age 64 years (range 50-78 years). One PS -2 mutation was identified in a sporadic case with onset age 62 years. Our mutation data provided estimates for PS -1 and PS -2 mutation frequencies in presenile AD of 6 and 1% respectively. When family history was accounted for mutation frequencies for PS -1 were 9% in familial cases and 18% in autosomal dominant cases. Further, polymorphisms were detected in the promoter and the 5'-non-coding region of PS -1 and in intronic and exonic **sequences** of PS -2 that will be useful in genetic association studies.

L26 ANSWER 55 OF 98 MEDLINE DUPLICATE 22
1998331525 Document Number: 98331525. Identification of a Drosophila presenilin homologue: evidence of alternatively spliced forms. Marfany G; Del-Favero J; Valero R; De Jonghe C; Woodrow S; Hendriks L; Van Broeckhoven C; Gonz`alez-Duarte R. (Departament de Gen`etica, Facultat de Biologia, Universitat de Barcelona, Spain.) JOURNAL OF NEUROGENETICS, (1998 Jan) 12 (1) 41-54. Journal code: JKE. ISSN: 0167-7063. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Some cases of **Alzheimer**'s disease are inherited as a dominant trait in humans. To date, mutations in three genes account for some of them: the amyloid precursor **protein** (APP) and presenilins 1 and

2 (PS-1 and PS-2, respectively). The function of the presenilins is still unclear, although they belong to a transmembrane **protein**-gene family, probably involved in some signaling pathway. We report here the isolation of the Drosophila presenilin homologue using the human PS-1 and PS-2 cDNAs as probes. Only one single gene has been detected in the Drosophila genome and evidence for alternatively spliced forms is presented and compared to the isoforms reported in humans. Temporal and spatial expression has been assessed by Northern blot and in situ hybridization on embryos of different developmental stages.

L26 ANSWER 56 OF 98 CAPLUS COPYRIGHT 2000 ACS
1998:523046 Document No. 129:273708 Molecular genetics of the presenilins in **Alzheimer**'s disease. **Fraser, P. E.**; Yu, G.; Levesque, G.; Ikeda, M.; Nishimura, M.; Rogaeva, E.; Westaway, D.; George-Hyslop, P. H. St.; Carlson, G. A. (Centre for Research in Neurodegenerative Disease, Department of Medicine, University of Toronto, Toronto, ON, M5S 1A8, Can.). Presenilins Alzheimer's Dis., 1-10. Editor(s): Younkin, Steven G.; Tanzi, Rudolph E.; Christen, Yves. Springer: Berlin, Germany. (English) 1998. CODEN: 66NEAP.

AB A review with 41 refs. The authors discuss mutations in the presenilin 1 and **presenilin 2** genes as well as other genes that are potentially involved in **Alzheimer**'s disease, the biol. of human presenilins, and animal models using presenilin **sequences**.

L26 ANSWER 57 OF 98 CAPLUS COPYRIGHT 2000 ACS
1997:684524 Document No. 127:357769 Study of variant **presenilin-2** genes and use of the variants for early diagnosis of **Alzheimer**'s disease. Hardy, John; Goate, Alison M.; Fuldner, Rebecca A. (University of South Florida, USA; Washington University; Institute of Genomic Research; Hardy, John; Goate, Alison M.; Fuldner, Rebecca A.). PCT Int. Appl. WO 9738133 A1 19971016, 39 pp. DESIGNATED STATES: W: AL, AM, AU, BB, BG, BR, CA, CN, CZ, EE, GE, GH, HU, IL, IS, JP, KG, KP, KR, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US4683 19970320. PRIORITY: US 1996-14860 19960404.

AB Variant **presenilin-2** genes that are highly assocd. with the onset of **Alzheimer**'s disease are characterized. **Presenilin-2** gene consists of 10 exons (numbered 3 to 12) and its exon/intron boundaries are elucidated. Two variant genes lacking (1) exons 3 and 4 and (2) exon 8, resp., due to alternate splicing are described. Methods of using these genes in diagnosing **Alzheimer**'s disease are also provided. The gene may be used to establish a model system for **Alzheimer**'s disease comprising variant **presenilin-2** genes.

L26 ANSWER 58 OF 98 MEDLINE DUPLICATE 23
1998019211 Document Number: 98019211. Evidence that levels of presenilins (PS1 and PS2) are coordinately regulated by competition for limiting cellular factors. Thinakaran G; Harris C L; Ratovitski T; Davenport F; Slunt H H; Price D L; Borchelt D R; Sisodia S S. (Department of Pathology, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205-2196, USA.. gopal@welchlink.welch.jhu.edu) . JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Nov 7) 272 (45) 28415-22. Journal code: HIV. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Mutations in two related genes, PS1 and PS2, account for the majority of early onset cases of familial **Alzheimer**'s disease. PS1 and PS2 are homologous polytopic membrane **proteins** that are processed endoproteolytically into two fragments in vivo. In the present report we examine the fate of endogenous PS1 and PS2 after overexpression of human PS1 or PS2 in mouse N2a neuroblastoma cell lines and human PS1 in transgenic mice. Remarkably, in N2a cell lines and in brains of transgenic mice expressing human PS1, accumulation of human PS1 derivatives is accompanied by a compensatory, and highly selective, decrease in the steady-state levels of murine PS1 and PS2 derivatives. Similarly, the levels of murine PS1 derivatives are diminished in cultured cells overexpressing human PS2. To define the minimal **sequence** requirements for "replacement" we expressed familial **Alzheimer**'s disease-linked and experimental deletion variants of PS1. These studies revealed that compromised accumulation of murine PS1 and PS2 derivatives resulting from overexpression of human PS1 occurs in a manner independent of endoproteolytic cleavage. Our results are consistent with a model in which the abundance of PS1 and PS2 fragments is regulated coordinately by competition for limiting cellular factor(s).

L26 ANSWER 59 OF 98 MEDLINE DUPLICATE 24
1998019198 Document Number: 98019198. Generation of anti-apoptotic **presenilin-2** polypeptides by alternative transcription, proteolysis, and caspase-3 cleavage. Vito P; Ghayur T; D'Adamio L. (T Cell Molecular Biology Unit, Laboratory of Cellular and Molecular Immunology, NIAID, National Institutes of Health, Bethesda, Maryland 20892, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 Nov 7) 272 (45) 28315-20. Journal code: HIV. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB PS2, the chromosome 1 familial **Alzheimer**'s disease gene, has been shown to be involved in programmed cell death by three complementary experimental approaches. Reduction of PS2 **protein** levels by antisense RNA protects from apoptosis, whereas overexpression of an **Alzheimer**'s PS2 mutant increases cell death induced by several stimuli. In addition, ALG-3, a truncated PS2 cDNA, encodes an artificial COOH-terminal PS2 segment that dominantly inhibits apoptosis. Here we describe a physiological COOH-terminal PS2 polypeptide (PS2s, Met298-Ile448) generated by both an alternative PS2 transcript and proteolytic cleavage. We find that PS2s protects transfected cells from Fas- and tumor necrosis factor alpha (TNFalpha)-induced apoptosis. Furthermore, a similar anti-apoptotic COOH-terminal PS2 polypeptide (PS2Ccas) is generated by caspase-3 cleavage at Asp329. These results suggest that caspase-3 not only activates pro-apoptotic substrates but also generates a negative feedback signal in which PS2Ccas antagonizes the progression of cell death. Thus, whereas PS2 is required for apoptosis, PS2s and PS2Ccas oppose this process, and the balance between PS2 and these COOH-terminal fragments may dictate the cell fate.

L26 ANSWER 60 OF 98 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
97256227 EMBASE Document No.: 1997256227. Presenilins are processed by caspase-type proteases. Loetscher H.; Deuschle U.; Brockhans M.; Reinhardt D.; Nelboeck P.; Mous J.; Grunberg J.; Haass C.; Jacobsen H.. H. Jacobsen, F. Hoffmann - La Roche Ltd., PRPN-G, Bldg. 66-709, Ch-4070 Basel, Switzerland. helmut.jacobsen@roche.com. Journal of Biological Chemistry 272/33 (20655-20659) 1997.
Refs: 28.

ISSN: 0021-9258. CODEN: JBCHA3. Pub. Country: United States. Language: English. Summary Language: English.

AB Presenilin 1 (PS1) and **presenilin 2** (PS2) are endoproteolytically processed in vivo and in cell transfectants to yield 27-35-kDa N-terminal and 15-24-kDa C-terminal fragments. We have studied the cleavage of PS1 and PS2 in transiently and stably transfected hamster kidney and mouse and human neuroblastoma cells by immunoblot and pulse-chase experiments. C-terminal fragments were isolated by affinity chromatography and SDS-polyacrylamide gel electrophoresis and **sequenced**. The processing sites identified in PS1 and PS2 (Asp345/Ser346 and Asp329/Ser330, respectively) are typical for caspase-type proteases. Specific caspase inhibitors and cleavage site mutations confirmed the involvement of caspase(s) in PS1 and PS2 processing in cell transfectants. Fluorescent peptide substrates carrying the PS- identified cleavage sites were hydrolyzed by proteolytic activity from mouse brain. The PS2-derived peptide substrate was also cleaved by recombinant human caspase-3. Additional processing of PS2 by non-caspase-type proteases was also observed.

L26 ANSWER 61 OF 98 MEDLINE DUPLICATE 25

1998054354 Document Number: 98054354. The seven-transmembrane spanning topography of the **Alzheimer** disease-related presenilin **proteins** in the plasma membranes of cultured cells. Dewji N N; Singer S J. (Department of Medicine, University of California at San Diego, La Jolla, CA 92093-0322, USA.. ndewji@ucsd.edu) . PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1997 Dec 9) 94 (25) 14025-30. Journal code: PV3. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB To ascertain the membrane topography of the multi-transmembrane spanning presenilin **proteins** PS-1 and PS-2, anti-peptide antibodies were raised to several specific amino acid **sequences** in the two **proteins**, and, after their specificity was ascertained, the anti-peptide antibodies were used in immunofluorescent labeling of live PS-transfected, cultured DAMI cells, which are impermeable to the antibodies, as well as of their fixed and permeabilized counterparts. In such experiments, antibodies that specifically stain the intact live cells must label epitopes of the PS **proteins** that are on the exterior face of the plasma membrane whereas those antibodies that do not stain the live cells but do stain the fixed and permeabilized cells must label epitopes that face the cytoplasmic side of the membrane. The results obtained were entirely in accord with the predictions of the seven-transmembrane spanning topography (like that of rhodopsin and the beta-adrenergic receptor) and were totally inconsistent with the expectations for either the six- or eight-transmembrane topographies that have been proposed.

L26 ANSWER 62 OF 98 MEDLINE

97277349 Document Number: 97277349. Evidence for a six-transmembrane domain structure of presenilin 1. Lehmann S; Chiesa R; Harris D A. (Department of Cell Biology and Physiology, Washington University School of Medicine, St. Louis, Missouri 63110, USA.) JOURNAL OF BIOLOGICAL CHEMISTRY, (1997 May 2) 272 (18) 12047-51. Journal code: HIV. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB Mutations in genes encoding presenilin 1 and **presenilin 2** account for the majority of cases of early-onset familial **Alzheimer**'s disease. The presenilins have been localized to the endoplasmic reticulum and Golgi, but which of the multiple hydrophobic

segments of the polypeptide chain span the lipid bilayer is unclear. To address this question, we have constructed a series of chimeric molecules in which a topologically neutral reporter **protein** (a C-terminal fragment of prolactin) containing three artificial glycosylation sites is fused to presenilin 1 following each of the 10 potential transmembrane domains identified in hydrophobicity plots. We have expressed these chimeras by translation in reticulocyte lysate containing canine pancreatic microsomes and by synthesis in transfected COS cells. Based on utilization of the glycosylation sites and sensitivity of the reporter to protease digestion, we provide evidence that presenilin 1 has six transmembrane segments with the N and C termini in the cytoplasm. This model provides important clues to the potential functions of different parts of the presenilin molecule and how these might relate to the pathogenesis of **Alzheimer**'s disease.

L26 ANSWER 63 OF 98 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
97129443 EMBASE Document No.: 1997129443. Endoproteolytic cleavage and proteasomal degradation of **presenilin 2** in transfected cells. Kim T.-W.; Pettingell W.H.; Hallmark O.G.; Moir R.D.; Wasco W.; Tanzi R.E.. R.E. Tanzi, Genetics and Aging Unit, Massachusetts General Hospital, 149 13th St., Charlestown, MA 02129, United States. tanzi@helix.mgh.harvard.edu. Journal of Biological Chemistry 272/17 (11006-11010) 1997.
Refs: 44.
ISSN: 0021-9258. CODEN: JBCHA3. Pub. Country: United States. Language: English. Summary Language: English.
AB Mutations in the presenilin genes, PS1 and PS2, cause a major portion of early onset familial **Alzheimer**'s disease (FAD). The biological roles of the presenilins and how their pathological mutations confer FAD are unknown. In this study, we set out to examine the processing and degradation pathways of PS2. For regulated expression of PS2, we have established inducible cell lines expressing PS2 under the tight control of the tetracycline-responsive transactivator. Western blot analysis revealed that PS2 was detected as an .apprx.53-55.kDa polypeptide (54.kDa PS2) as well as a high molecular mass form (HMW-PS2). Using a stably transfected, inducible cell system, we have found that PS2 is proteolytically cleaved into two stable cellular polypeptides including an 20-kDa C-terminal fragment and an .apprx.34-kDa N-terminal fragment. PS2 is polyubiquitinated in vivo, and the degradation of PS2 is inhibited by proteasome inhibitors, N-acetyl-L-leucinal-L-norleucinal and lactacystin. Our studies suggest that PS2 normally undergoes endoproteolytic cleavage and is degraded via the proteasome pathway.

L26 ANSWER 64 OF 98 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.
97095958 EMBASE Document No.: 1997095958. Enhanced production and oligomerization of the 42-residue amyloid .beta.- **protein** by chinese hamster ovary cells stably expressing mutant presenilins. Xia W.; Zhang J.; Kholodenko D.; Citron M.; Podlisny M.B.; Teplow D.B.; Haass C.; Seubert P.; Koo E.H.; Selkoe D.J.. D.J. Selkoe, Department of Neurology, Harvard Medical School, Brigham and Women's Hospital, Boston, MA 02115, United States. selkoe@cnd.bwh.harvard.edu. Journal of Biological Chemistry 272/12 (7977-7982) 1997.
Refs: 47.
ISSN: 0021-9258. CODEN: JBCHA3. Pub. Country: United States. Language: English. Summary Language: English.
AB Mutations in the presenilin 1 (PS1) and **presenilin 2** (PS2) genes cause the most common and aggressive form of early onset familial **Alzheimer**'s disease. To elucidate their pathogenic

mechanism, wild-type (wt) or mutant (M146L, C410Y) PS1 and wt or mutant (M239V) PS2 genes were stably transfected into Chinese hamster ovary cells that overexpress the .beta.-amyloid precursor **protein** (APP). The identity of the 43-45-kDa PSI holoproteins was confirmed by N-terminal radiosequencing. PSI was rapidly processed (t(1/2) = 40 min) in the endoplasmic reticulum into stable fragments. Wild-type and mutant PS2 holoproteins exhibited similar half lives (1.5 h); however, their endoproteolytic fragments showed both mutation-specific and cell type-specific differences. Mutant PS1 or PS2 consistently induced a 1.4-2.5-fold increase ($p < 0.001$) in the relative production of the highly amyloidogenic 42-residue form of amyloid .beta.-**protein** (A.beta.42) as determined by quantitative immunoprecipitation and by enzyme-linked immunosorbent assay. In mutant PS1 and PS2 cell lines with high increases in A.beta.42/A.beta.(total) ratios, spontaneous formation of low molecular weight oligomers of A.beta.42 was observed in media, suggesting enhanced A.beta. aggregation from the elevation of A.beta.42. We conclude that mutant PS1 and PS2 **proteins** enhance the proteolysis of .beta.-amyloid precursor **protein** by the .gamma.-secretase cleaving at A.beta. residue 42, thereby promoting amyloidogenesis.

L26 ANSWER 65 OF 98 EMBASE COPYRIGHT 2000 ELSEVIER SCI. B.V.

97288654 EMBASE Document No.: 1997288654. The presenilins and **Alzheimer**'s disease. Hutton M.; Hardy J.. M. Hutton, Neurogenetics Laboratory, The Mayo Clinic Jacksonville, 4500 San Pablo Road, Jacksonville, FL 32224, United States. hutton.michael@mayo.edu. Human Molecular Genetics 6/10 REV. ISS. (1639-1646) 1997.
Refs: 70.
ISSN: 0964-6906. CODEN: HMGEE5. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB The presenilin 1 and **presenilin 2** genes have been identified as pathogenic loci involved in the majority of early onset, autosomal dominant **Alzheimer**'s disease. A series of (predominantly) missense mutations have been identified in the two genes which lead to disease. The presenilins are probably eight transmembrane domain **proteins** with both termini in the cytoplasmic compartment. They have a wide tissue distribution and are found in the endoplasmic reticulum and early Golgi. The mechanism of pathogenesis of the mutations is not clear although, both in patients and in in vitro systems, the effects of presenilin mutations are reminiscent of the effects of the pathogenic mutations in the amyloid precursor **protein** gene which lead to increases in the amount of amyloid-.beta.42(43) being produced from the metabolism of the amyloid **protein** precursor. Thus, the presenilin data provide independent support for the amyloid cascade hypothesis of **Alzheimer**'s pathogenesis. Work on the Caenorhabditis elegans homologues of the presenilins, spe-4 and sel-12, suggests that the presenilins may have a more general and direct role in the processing and trafficking of membrane-bound **proteins** and that, in part, the pathogenic mutations may disrupt this role.

L26 ANSWER 66 OF 98 MEDLINE

97285868 Document Number: 97285868. Cloning and characterization of the Drosophila presenilin homologue. Boulianne G L; Livne-Bar I; Humphreys J M; Liang Y; Lin C; Rogaev E; **St. George-Hyslop P.** (Hospital for Sick Children, Department of Physiology and Zoology, University of Toronto, Ontario, Canada.) NEUROREPORT, (1997 Mar 3) 8 (4) 1025-9.
Journal code: A6M. ISSN: 0959-4965. Pub. country: ENGLAND: United Kingdom.

Language: English.

AB Mutations in two genes, PS1 and PS2, coding for the presenilins, have been linked to the early onset form of familial **Alzheimer**'s disease (AD). Here we report the identification of a Drosophila melanogaster homologue of human PS genes, Dps, which maps to band 77B-C on chromosome 3 and is expressed at multiple developmental stages. The predicted amino acid **sequence** of the Dps product is 53% identical to human presenilins, with the greatest similarity in the putative transmembrane domains, the hydrophobic domains at the beginning and the end of the cytoplasmic TM6-TM7 loop and the C-terminus. Analysis of Dps in a genetically tractable model system such as Drosophila may provide insight into the mechanisms of **Alzheimer**'s disease (AD) necessary for the development of rational therapeutic approaches.

L26 ANSWER 67 OF 98 CAPLUS COPYRIGHT 2000 ACS

1998:185304 Document No. 128:306878 Molecular biology of **Alzheimer**'s disease. Mori, Hiroshi (Dep. of Molecular Biology, Tokyo Institute of Psychiatry, Tokyo, 156, Japan). Shinkei Kenkyu no Shinpo, 41(6), 859-865 (Japanese) 1997. CODEN: SKNSAF. ISSN: 0001-8724. Publisher: Igaku Shoin Ltd..

AB A review with 23 refs. **Alzheimer**'s disease (AD) is the most common cause of progressive intellectual failure in aged people. In addn. to APP localized on human chromosome 21, the major causal gene of early-onset familial AD was identified as presenilin 1 (PS-1) localized on 14q24.3. The final identification of PS-1 as the causal gene for **Alzheimer**'s disease was concluded based on finding of the point mutations in the candidate cDNA linked with pedigrees with early-onset familial AD. PS-1 is predicted to encode a 467 amino acid **protein** from the deduced ORF of the cDNA. A homologous gene, **presenilin 2** was identified in a Volga-German pedigrees with a high incidence of another form of early-onset familial AD, which was localized on chromosome 1q42.1. Both **proteins** encoded by these two genes were predicted to share seven or nine transmembrane (TM) domains and one cytoplasmic loop structure between TM6 and TM7 as deduced from their nucleotide **sequences**. Apolipoprotein E allele .epsilon. 4 was established to be a risk factor which accounts for about half portion of total AD patients despite of its minor distribution in human populations. Here, I describe the effect of these causal genes or risk factors on cerebral A.beta. deposition, in particularly based on two A.beta. species of A.beta.42/43 and A.beta.40, A.beta.42/43 and A.beta. 40 was found to be linked with early-onset and late-onset AD, supporting seeding theory by which A.beta.42/43 and A.beta.40 were involved in the initial and late/elongation reactions of amyloid fibril formation, resp. Hence, amyloid deposition was concluded to be a specific phenotype to reflect genetic alterations as well as neuropathol. of AD.

L26 ANSWER 68 OF 98 MEDLINE DUPLICATE 26

1998063306 Document Number: 98063306. Determination of a cleavage site of **presenilin 2 protein** in stably transfected SH-SY5Y human neuroblastoma cell lines. Shirotani K; Takahashi K; Ozawa K; Kunishita T; Tabira T. (Division of Demyelinating Disease and Aging, National Institute of Neuroscience, Tokyo, Japan.) BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1997 Nov 26) 240 (3) 728-31. Journal code: 9Y8. ISSN: 0006-291X. Pub. country: United States. Language:

English.

AB Mutations in the presenilin 1 (PS1) and **presenilin 2** (PS2) genes are associated with early-onset autosomal dominant familial **Alzheimer**'s disease, and the gene products are endoproteolytically processed to yield N-terminal fragments (NTF) and C-terminal fragments (CTF). We have studied the cleavage site of the PS2 **protein** in stably transfected human neuroblastoma cells. The 23 kD PS2-CTF was isolated by a combination of anion exchange chromatography and affinity chromatography and directly **sequenced**. The N-terminus of the PS2-CTF started at residue 307, which indicated that the cleavage occurs between Lys306 and Leu307 in the proximal portion of the large hydrophilic loop. This site is close to the cleavage positions observed in the PS1 **protein**.

L26 ANSWER 69 OF 98 MEDLINE DUPLICATE 27

97260623 Document Number: 97260623. Isolation and characterization of Drosophila presenilin homolog. Hong C S; Koo E H. (Department of Neurology, Harvard Medical School, Boston MA 02115, USA.) NEUROREPORT, (1997 Feb 10) 8 (3) 665-8. Journal code: A6M. ISSN: 0959-4965. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Presenilin-1 (PS1) and **presenilin-2** (PS2) are associated with a majority of early onset familial **Alzheimer**'s disease (FAD). **Sequence** analysis of PS1/2 has revealed integral transmembrane **proteins** which are highly homologous to the **protein** coded by sel-12, a Caenorhabditis elegans gene involved in the lin-12/Notch signaling pathway. The normal function of PS1/2, as well as the pathogenesis caused by mutations of these genes in FAD, are unknown however. We have identified a Drosophila presenilin homolog (DPS) and mapped the chromosomal location of this gene. DPS shows 53% amino acid identity to PS1/2 and 45% to the sel-12 product. Strong amino acid conservations appear at the position associated with FAD. In embryonic stages, DPS is expressed primarily in the CNS.

L26 ANSWER 70 OF 98 MEDLINE

97360063 Document Number: 97360063. Regional and cellular localization of **presenilin-2** RNA in rat and human brain. Benkovic S A; McGowan E M; Rothwell N J; Hutton M; Morgan D G; Gordon M N. (Department of Pharmacology, University of South Florida, Tampa 33612-4799, USA.) EXPERIMENTAL NEUROLOGY, (1997 Jun) 145 (2 Pt 1) 555-64. Journal code: EQF. ISSN: 0014-4886. Pub. country: United States. Language: English.

AB In situ hybridization probes selective for **presenilin-2** (PS-2) were used to determine the regional and cellular expression pattern of PS-2 mRNA in rat and human brain. In rat brain, the greatest expression of PS-2 mRNA is in the granule cell layers of the dentate gyrus and cerebellum. Molecular layers within these structures are virtually devoid of signal. Cortical expression of PS-2 message is restricted to neuronal layers, while the hybridization signal is weak or absent in molecular layers and white matter. Kidney, liver, and spleen display moderate levels of PS-2 message. A PS-2 sense strand probe produced no specific signals in any tissue. In human brain, the greatest hybridization signal for PS-2 is present in the granule cells of the cerebellum. Within hippocampus, the granule cell layer of dentate is strongly labeled, with CA3 pyramidal neurons also clearly visible. A laminar expression pattern is seen in the neuronal layers of human frontal and temporal cortex, with the deeper laminae having the strongest signals. These data are consistent with a

primarily neuronal localization of PS-2 mRNA within the brains of both rat and human. Within the limitations of the analysis, it appears that virtually every neuron is labeled, and differences in the intensity of labeling are associated with both neuron size/density and brain region. The distribution of PS-2 RNA is not restricted to those regions having the greatest pathology in **Alzheimer**'s disease. However, one unusual pathological feature of PS-2 mutations causing AD is the presence of cerebellar amyloid plaques in some cases. It is intriguing, in this context, that PS-2 RNA is enriched in the cerebellum, especially in human specimens.

L26 ANSWER 71 OF 98 MEDLINE DUPLICATE 28
97477394 Document Number: 97477394. Increased apoptosis arising from increased expression of the **Alzheimer**'s disease-associated **presenilin-2** mutation (N141I). Janicki S; Monteiro M J. (Medical Biotechnology Center of the University of Maryland Biotechnology Institute, Baltimore, Maryland 21201, USA.) JOURNAL OF CELL BIOLOGY, (1997 Oct 20) 139 (2) 485-95. Journal code: HMV. ISSN: 0021-9525. Pub. country: United States. Language: English.

AB Mutations in the genes for presenilin 1 and 2 (PS-1 and PS-2) have been linked to development of early-onset **Alzheimer**'s disease (AD). As neither the normal function of either presenilin is known nor why mutations cause disease, we examined the properties of wild-type, truncated, and mutant PS-2 upon expression in HeLa cells. Although HeLa cells are strongly predisposed to continued mitosis, expression of PS-2 induced programmed cell death (apoptosis). Direct evidence for apoptosis was obtained by double staining for terminal deoxynucleotide transferase nick end labeling (TUNEL) and PS-2 expression and by following green fluorescent **protein**-tagged PS-2 over time. Deletion analysis indicates that as little as 166 NH2-terminal residues of PS-2 are sufficient for endoplasmic reticulum (ER) localization and apoptosis. Moreover, the AD- associated PS-2 missense mutation (N141I) more efficiently induced cell death compared to wild-type PS-2 despite lower mutant **protein** accumulation. Expression of the presenilins in several other cell lines and transgenic mice has been accompanied by rapid **protein** cleavage without the induction of cell death. In contrast, PS-2 expressed in HeLa cells was not cleaved, and cell death occurred. We hypothesize that full-length but not cleaved PS-2 may be important in the regulation or induction of apoptosis.

L26 ANSWER 72 OF 98 MEDLINE DUPLICATE 29
97473536 Document Number: 97473536. Cloning of cDNA and expression of the gene encoding rat **presenilin-2**. Takahashi H; Mercken M; Nakazato Y; Noguchi K; Murayama M; Imahori K; Takashima A. (Mitsubishi Kasei Institute of Life Sciences, Tokyo, Japan.) GENE, (1997 Sep 15) 197 (1-2) 383-7. Journal code: FOP. ISSN: 0378-1119. Pub. country: Netherlands. Language: English.

AB We have cloned the rat homologue of the **presenilin-2** (PS-2) cDNA. PS-2 is responsible for chromosome 1-linked familial **Alzheimer**'s disease. **Sequence** analysis predicted that the rat PS-2 encodes a 448 amino acid (aa) **protein**, and there was a very high degree of amino acid identity between rat and human PS-2 (95%). All the mutated codons in PS-2 and PS-1 in chromosome 1- or 14-linked familial **Alzheimer**'s disease patients were conserved in rat PS-2. The expression of PS-2 was weaker than that of PS-1. The alternatively spliced short form of PS-2 mRNA, which was detected in human tissues was not detected in various rat tissues. During brain development,

the expression level of both PS-2 and PS-1 increased but decreased in the adult. No remarkable change was observed in neural differentiation of PC12 cells.

L26 ANSWER 73 OF 98 MEDLINE
97317150 Document Number: 97317150. Presenilin **proteins** undergo heterogeneous endoproteolysis between Thr291 and Ala299 and occur as stable N- and C-terminal fragments in normal and **Alzheimer** brain tissue. Podlisny M B; Citron M; Amarante P; Sherrington R; Xia W; Zhang J; Diehl T; Levesque G; **Fraser P**; Haass C; Koo E H; Seubert P; **St. George-Hyslop P**; Teplow D B; Selkoe D J. (Center for Neurologic Diseases, Harvard Medical School, Boston, Massachusetts, 02115, USA.) NEUROBIOLOGY OF DISEASE, (1997) 3 (4) 325-37. Journal code: CUN. ISSN: 0969-9961. Pub. country: United States. Language: English.
AB Humans inheriting missense mutations in the presenilin (PS)1 and -2 genes undergo progressive cerebral deposition of the amyloid beta-**protein** at an early age and develop a clinically and pathologically severe form of familial **Alzheimer**'s disease (FAD). Because PS1 mutations cause the most aggressive known form of AD, it is important to elucidate the structure and function of this multitransmembrane **protein** in the brain. Using a panel of region-specific PS antibodies, we characterized the presenilin polypeptides in mammalian tissues, including brains of normal, AD, and PS1-linked FAD subjects, and in transfected and nontransfected cell lines. Very little full-length PS1 or -2 was detected in brain and untransfected cells; instead the **protein** occurred as a heterogeneous array of stable N- and C-terminal proteolytic fragments that differed subtly among cell types and mammalian tissues. Sequencing of the major C-terminal fragment from PS1-transfected human 293 cells showed that the principal endoproteolytic cleavage occurs at and near Met298 in the proximal portion of the large hydrophilic loop. Full-length PS1 in these cells is quickly turned over (T1/2 approximately 60 min), in part to the two major fragments. The sizes and amounts of the PS fragments were not significantly altered in four FAD brains with the Cys410Tyr PS1 missense mutation. Our results indicate that presenilins are rapidly processed to N- and C-terminal fragments in both neural and nonneural cells and that interference with this processing is not an obligatory feature of FAD-causing mutations.

L26 ANSWER 74 OF 98 MEDLINE DUPLICATE 30
97347186 Document Number: 97347186. Immunohistochemical analysis of **presenilin 2** expression in the mouse brain: distribution pattern and co-localization with presenilin 1 **protein**. Blanchard V; Czech C; Bonici B; Clavel N; Gohin M; Dalet K; Revah F; Pradier L; Imperato A; Moussaoui S. (Rhone-Poulenc Rorer, Centre de Recherche de Vitry-Alfortville, Vitry-sur-Seine, France.) BRAIN RESEARCH, (1997 May 30) 758 (1-2) 209-17. Journal code: B5L. ISSN: 0006-8993. Pub. country: Netherlands. Language: English.
AB Missense mutations of presenilin 1 (PS-1) and **presenilin 2** (PS-2) genes cause the majority of early-onset familial forms of **Alzheimer**'s disease (AD). We previously characterized the distribution of the PS-1 **protein** in the mouse brain by immunohistochemistry using an antibody directed against an epitope located in the large hydrophilic loop [Moussaoui, S., Czech, C., Pradier, L., Blanchard, V., Bonici, B., Gohin, M., Imperato, A. and Revah, F.,

Immunohistochemical analysis of presenilin 1 expression in the mouse brain, FEBS Lett., 383 (1996) 219-222]. Similarly, we now report the distribution pattern of PS-2 **protein** in the mouse brain. For these experiments we used a polyclonal antibody raised against a synthetic peptide corresponding to the amino-acid **sequence** 7-24 of the predicted human PS-2 **protein**. The specificity of the antibody was evidenced by its ability to recognize PS-2 **protein** in immunoprecipitation studies and by antigen-peptide competition. In the mouse brain, PS-2 **protein** was present in numerous cerebral structures, but its distribution in these structures did not correlate with their susceptibility to AD pathology. In all examined structures of the gray matter, PS-2 **protein** was concentrated in neuronal cell bodies but it was not detected in the glial cells of the white matter. The regional distribution pattern of PS-2 **protein** was almost identical to that of PS-1 **protein**. Moreover, PS-2 **protein** co-localized with PS-1 **protein** in a large number of neuronal cell bodies. In terms of subcellular localization, PS-2 immunostaining was present almost exclusively in neuronal cell bodies while PS-1 immunostaining was also present in dendrites. This could be explained by the different epitopes of the antibodies and the known proteolytic processing of both presenilins in vivo [Tanzi, R.E., Kovacs, D.M., Kim, T.-W., Moir, R.D., Guenette, S.Y. and Wasco, W., The presenilin genes and their role in early-onset familial **Alzheimer**'s disease, **Alzheimer**'s disease Rev., 1 (1996) 91-98]. Within neuronal cell bodies, the immunostaining of PS-2 **protein**, as well as that of PS-1 **protein**, had a reticular and granular appearance. This suggests in agreement with previous observations on PS-1 and PS-2 in COS and H4 cells [Kovacs, D.M., Fausett, H.J., Page, K.J., Kim, T.-W., Moir, R.D., Merriam, D.E., Hollister, R.D., Hallmark, O.G., Mancini, R., Felsenstein, K.M., Hyman, B.T., Tanzi, R.E., Wasco, W., **Alzheimer**-associated presenilins 1 and 2: neuronal expression in brain and localization to intracellular membranes in mammalian cells, Nature Med., 2 (1996) 224-229] that these **proteins** are situated in intracytoplasmic organelles, possibly the endoplasmic reticulum and the Golgi complex.

L26 ANSWER 75 OF 98 MEDLINE DUPLICATE 31
1998074929 Document Number: 98074929. Proteolytic processing of presenilin-1 (PS-1) is not associated with **Alzheimer**'s disease with or without PS-1 mutations. Okochi M; Ishii K; Usami M; Sahara N; Kametani F; Tanaka K; **Fraser P E**; Ikeda M; Saunders A M; Hendriks L; Shoji S I; Nee L E; Martin J J; Van Broeckhoven C; **St. George-Hyslop P H**; Roses A D; Mori H. (Department of Molecular Biology, Tokyo Institute of Psychiatry, Japan.) FEBS LETTERS, (1997 Nov 24) 418 (1-2) 162-6. Journal code: EUH. ISSN: 0014-5793. Pub. country: Netherlands. Language: English.

AB Cerebral presenilin-1 **protein** (PS-1) is normally composed of the amino-terminal fragment (NTF) with Mr 28 kDa and the carboxy-terminal fragment (CTF) with 18 kDa. We analyzed human PS-1 in brains with early-onset familial **Alzheimer**'s disease (FAD) with and without PS-1 mutations to study whether mutated PS-1 was abnormally metabolized. Cerebral PS-1 were found to be cleaved into two fragments of NTF and CTF independently of the occurrence of PS-1 mutation in human brains. A small portion of PS-1 was recently found to suffer another processing by caspase-3, an apoptosis-related cysteine protease. In contrast to the recent finding that the Volga-German mutation on **presenilin**-

2 (PS-2) affects the increasing caspase-3 PS-2 fragment, the PS-1 mutation did not cause a significant change in PS-1 fragmentation. We conclude that PS-1 fragmentation and other (probably caspase-3-mediated) digestion following apoptosis occur independently of PS-1 mutations.

L26 ANSWER 76 OF 98 MEDLINE
97369208 Document Number: 97369208. Early-onset **Alzheimer**'s disease with a presenilin-1 mutation at the site corresponding to the Volga German **presenilin-2** mutation. Crook R; Ellis R; Shanks M; Thal L J; Perez-Tur J; Baker M; Hutton M; Haltia T; Hardy J; Galasko D. (Department of Psychiatry, University of South Florida, Tampa, USA.) ANNALS OF NEUROLOGY, (1997 Jul) 42 (1) 124-8. Journal code: 6AE. ISSN: 0364-5134. Pub. country: United States. Language: English.
AB We describe a new mutation causing **Alzheimer**'s disease (AD) in presenilin-1 (N135D) that is at the homologous site to the **presenilin 2** mutation (N141I) in Volga German kindreds. The phenotype of PS1 N135D is an early-onset (34-38 years) disease. The mutation forms part of, and extends, the alpha-helical array of mutations in transmembrane 2 of the presenilins and leads to the suggestion that disruption of this helical face is the molecular insult that leads to disease.

L26 ANSWER 77 OF 98 CAPLUS COPYRIGHT 2000 ACS
1997:227180 Document No. 126:275586 Biology of presenilin 1 and **presenilin 2**. Mori, Hiroshi (Dep. Molecular Biology, Tokyo Inst. Psychiatry, Tokyo, 156, Japan). Shinkei Kenkyu no Shinpo, 41(1), 18-28 (Japanese) 1997. CODEN: SKNSAF. ISSN: 0001-8724. Publisher: Igaku Shoin.
AB A review, with 32 refs. **Alzheimer**'s disease (AD) is the most common cause of progressive intellectual failure in aged people. In addn. to APP localized on human chromosome 21, the major causal gene of early-onset familial AD was identified as presenilin 1 (PS 1) localized on 14q24.3. The final identification of PS 1 as the causal gene for **Alzheimer**'s disease was concluded based on finding of the point mutations in the candidate cDNA linked with pedigrees with early-onset familial AD. PS 1 is predicted to encode a 467 amino acid **protein** from the deduced ORF of the cDNA. A homologous gene, **presenilin 2** was identified in a Volga-German pedigree with a high incidence of another form of eraly-onset familial AD. Both **proteins** encoded by these two genes were predicted to share 7 transmembrane (TM) domains and one loop structure between TM6 and TM7 as deduced from their nucleotide **sequences**. Here, I describe the abnormal behavior of PS 1 in gel electrophoresis in the presence of SDS. Freshly in vitro synthesized PS 1 was identified as a single mol. with the mol. size of 44,000 on SDS gels but was found to disappear after incubation at 37.degree.C for 24 h due to the formation of aggregates. Intermediate aggregates with mr 74,000 and 100,000 were formed before the final aggregate which was retained at the top of the gel. Thus the amt. of 43,000-**protein** species of PS 1 was found to decrease on gels with a concomitant increase in the amt. of 74,000/100,000 **proteins**. Similar abnormality was seen in PS 1 expressed in COS cells transfected with PS 1 cDNA. Moreover, cellular PS 1 was strongly suggested to be cleaved into the fragments with mr 26,000 and 20,000 in COS cells. Such fragments of PS 1 were obsd. in human brains with or without PS 1 mutations, indicating that fragmentation was not the crucial reaction in the brain. Full-sized presenilin and its possible deriv. may play a role in cell surviving against apoptosis and neurotoxicity induced by amyloid .beta. **protein**.

L26 ANSWER 78 OF 98 MEDLINE
1998006155 Document Number: 98006155. A novel pathogenic mutation (Leu262Phe) found in the presenilin 1 gene in early-onset **Alzheimer**'s disease. Forsell C; Froelich S; Axelman K; Vestling M; Cowburn R F; Lilius L; Johnston J A; Engvall B; Johansson K; Dahlkild A; Ingelson M; **St. George-Hyslop P H**; Lannfelt L. (Karolinska Institute, Department of Geriatric Medicine, Huddinge University Hospital, Novum, Sweden.) NEUROSCIENCE LETTERS, (1997 Sep 26) 234 (1) 3-6. Journal code: N7N. ISSN: 0304-3940. Pub. country: Ireland. Language: English.

AB Several mutations causing early-onset familial **Alzheimer**'s disease (AD) have been detected in the presenilin 1 (PS-1) gene. Pathogenic mutations have also been described in an homologous gene, **presenilin 2** (PS-2). In order to screen for mutations in these genes, cDNA samples from early-onset AD cases were analysed, using single strand conformation polymorphism (SSCP) and direct cDNA sequencing.

Two missense mutations in the PS-1 gene were detected, a previously unidentified amino acid substitution Leu262Phe and an earlier reported amino acid substitution Glu318Gly. No disease-related mutations were found in the PS-2 gene.

L26 ANSWER 79 OF 98 BIOSIS COPYRIGHT 2000 BIOSIS
1997:348249 Document No.: PREV199799647452. Presenilins and early-onset familial **Alzheimer**'s disease. Rohan De Silva, H. A. (1); Patel, Ambrish J.. (1) MRC Neurodegenerative Disorders Group, Dep. Biochem., Charing Cross Westminster Med. Sch., Fulham Palace Rd., London W6 8RF UK. Neuroreport, (1997) Vol. 8, No. 8, pp. I-XII. ISSN: 0959-4965. Language: English.

AB Thirty-seven missense mutations and a splice-site mutation in the presenilin gene PS1 on chromosome 14 and two missense mutations PS2 on chromosome 1 co-segregate with early-onset familial **Alzheimer**'s disease (AD). The presenilins belong to a family of conserved integral membrane **proteins** which include Caenorhabditis elegans SPE4 and SEL12 and the rat apoptosis-linked gene, ALG3. This review summarizes the genetics of presenilins in AD and indicators of putative function based on cellular localization and the functions of non-human homologues. Findings to date suggest an important role of presenilins in beta-amyloid (A-beta) production: in vitro and in vivo studies have shown that presenilin mutations are associated with relatively increased production of the longer, and highly fibrillogenic A-beta-42(43) peptide, and a marked elevation in the number of A-beta-42-immunoreactive plaques in the brains of individuals with familial AD who carry PS1 and PS2 mutations. There is growing evidence that the deposition of A-beta-42(43) could in some cases be an early and key event in the AD pathogenic cascade. The genetic and molecular biological data discussed in this review describe mechanisms by which presenilin mutations could lead to the development of AD. Also, mutant presenilins may be more pro-apoptotic. It is argued that the understanding of the processes by which presenilin mutations lead to the development of AD will help in devising a coherent framework for therapeutic strategies.

L26 ANSWER 80 OF 98 CAPLUS COPYRIGHT 2000 ACS
1997:9243 Document No. 126:27685 Human, mouse, and Drosophila presenilin cDNA and gene **sequences**, mutants related to **Alzheimer**'s disease, and disease modeling, diagnosis, gene therapy, and immunotherapy. **St, George-Hyslop Peter H.**; Fraser, Paul E.;

Rommens, Johanna M. (Hsc Research and Development Limited Partnership, Can.; Governing Council of the University of Toronto; St. George-Hyslop, Peter H.; Fraser, Paul E.; Rommens, Johanna M.). PCT Int. Appl. WO 9634099 A2 19961031, 178 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1996-CA263 19960429. PRIORITY: US 1995-431048 19950428; US 1995-496841 19950628; US 1995-509359
19950731.

AB The present invention describes the identification, isolation, sequencing and characterization of two human presenilin genes. PS-1 and PS-2 mutations lead to familial **Alzheimer**'s disease. Also identified are presenilin gene homologs in mice, C. elegans, and D. melanogaster. Nucleic acids and **proteins** comprising or derived from the presenilins are useful in screening and diagnosing **Alzheimer**'s disease, in identifying and developing therapeutics for treatment of **Alzheimer**'s disease, and in producing cell lines and transgenic animals useful as models of **Alzheimer**'s disease.

L26 ANSWER 81 OF 98 MEDLINE DUPLICATE 32

97094860 Document Number: 97094860. Requirement of the familial **Alzheimer**'s disease gene PS2 for apoptosis. Opposing effect of ALG-3. Vito P; Wolozin B; Ganjei J K; Iwasaki K; Lacana E; D'Adamio L. (T-Cell Molecular Biology Unit, Laboratory of Cellular and Molecular Immunology, NIAID, National Institutes of Health, Maryland 20892, USA.. ldadamio@atlas.niaid.nih.gov) . JOURNAL OF BIOLOGICAL CHEMISTRY, (1996 Dec
6) 271 (49) 31025-8. Journal code: HIV. ISSN: 0021-9258. Pub. country: United States. Language: English.

AB ALG-3, a truncated mouse homologue of the chromosome 1 familial **Alzheimer**'s disease gene PS2, rescues T hybridoma 3DO cells from T-cell receptor-induced apoptosis by inhibiting Fas ligand induction and Fas signaling. Here we show that ALG-3 transfected 3DO cells express a COOH-terminal PS2 polypeptide. Overexpression of PS2 in ALG-3 transfected 3DO cells reconstitutes sensitivity to receptor-induced cell death, suggesting that the artificial PS2 polypeptide functions as a dominant negative mutant of PS2. ALG-3 and antisense PS2 protect PC12 cells from glutamate-induced apoptosis but not from death induced by hydrogen peroxide or the free radical MPP+. Thus, the PS2 gene is required for some
forms of cell death in diverse cell types, and its function is opposed by ALG-3.

L26 ANSWER 82 OF 98 MEDLINE

97121494 Document Number: 97121494. Assessment of normal and mutant human presenilin function in Caenorhabditis elegans. Levitan D; Doyle T G; Brousseau D; Lee M K; Thinakaran G; Slunt H H; Sisodia S S; Greenwald I. (Howard Hughes Medical Institute, College of Physicans and Surgeons, Columbia University, New York, NY 10032, USA.) PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1996 Dec 10) 93 (25) 14940-4. Journal code: PV3. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB We provide evidence that normal human presenilins can substitute for Caenorhabditis elegans SEL-12 **protein** in functional assays in vivo. In addition, six familial **Alzheimer** disease-linked mutant human presenilins were tested and found to have reduced ability to rescue the sel-12 mutant phenotype, suggesting that they have lower than normal presenilin activity. A human presenilin 1 deletion variant that fails to

be proteolytically processed and a mutant SEL-12 **protein** that lacks the C terminus display considerable activity in this assay, suggesting that neither presenilin proteolysis nor the C terminus is absolutely required for normal presenilin function. We also show that sel-12 is expressed in most neural and nonneural cell types in all developmental stages. The reduced activity of mutant presenilins and as yet unknown gain-of-function properties may be a contributing factor in the development of **Alzheimer** disease.

L26 ANSWER 83 OF 98 CAPLUS COPYRIGHT 2000 ACS
1996:665395 Document No. 125:323920 Specific transcellular binding between membrane **proteins** crucial to **Alzheimer** disease.
Dewji, Nazneen N.; Singer, S. J. (Dep. Med. Biol., Univ. California, San Diego, La Jolla, CA, 92093, USA). Proc. Natl. Acad. Sci. U. S. A., 93(22), 12575-12580 (English) 1996. CODEN: PNASA6. ISSN: 0027-8424.
AB Mol. genetic studies of families suffering from genetic forms of early onset **Alzheimer** disease (AD) have identified three genes and their **protein** products as being crucially involved in the etiol. of AD. The three **proteins** are all integral membrane **proteins**. One of them is .beta.-APP, the precursor of the .beta.-amyloid found in the characteristic neuritic plaques present in the brains of AD patients. The other two, S182 and STM2, are homologous in amino acid **sequence** to one another but are unrelated to .beta.-APP. It is shown here, using cultured cells transfected for each of these **proteins**, that .beta.-APP binds specifically and transcellularly to either S182 or STM2. The authors propose that this transcellular binding may not only be important in normal neuronal physiol. and development but may be directly involved in the process of formation of .beta.-amyloid from .beta.-APP.

L26 ANSWER 84 OF 98 MEDLINE
97061686 Document Number: 97061686. A presenilin 1 mutation in an early onset **Alzheimer**'s family: no association with **presenilin 2**. Poduslo S E; Herring K; Neal M. (Department of Neurology, Texas Tech University, Health Sciences Center, Lubbock 79430, USA.) NEUROREPORT, (1996 Aug 12) 7 (12) 2018-20. Journal code: A6M. ISSN: 0959-4965. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Genes on four chromosomes have been associated with **Alzheimer**'s disease. Mutations in the chromosome 14 gene (S182 or presenilin 1) have been linked with an aggressive very early form of the disease while mutations in a chromosome 1 gene (STM2 or **presenilin 2**) have been linked with Volga German kindreds. When we screened our **Alzheimer**'s patients for the first mutations reported, we only found one in the presenilin 1 gene in an extended family with three affected siblings, all of whom had onset of symptoms in their 4Cs. ApoE and ApoCI genotyping indicated that these risk factors were not associated with the disease in this family. None of our patients with early or late onset disease had the mutation described for **presenilin 2**.

L26 ANSWER 85 OF 98 MEDLINE DUPLICATE 33
97110360 Document Number: 97110360. Antibodies to presenilin **proteins** detect neurofibrillary tangles in **Alzheimer**'s disease. Murphy G M Jr; Forno L S; Ellis W G; Nochlin D; Levy-Lahad E; Poorkaj P; Bird T D; Jiang Z; Cordell B. (Department of Psychiatry and Behavioral Sciences, Stanford University Medical Center, California, USA.) AMERICAN JOURNAL OF PATHOLOGY, (1996 Dec) 149 (6) 1839-46. Journal code: 3RS. ISSN: 0002-9440. Pub. country: United States. Language: English.

AB Mutations in the presenilin (PS)-1 and PS-2 genes have been shown to be linked with the development of **Alzheimer**'s disease (AD). We examined **Alzheimer**'s brain tissue by immunohistochemistry using a set of antibodies raised to **sequences** shared between PS-1 and PS-2 **proteins**. These antibodies reacted exclusively with a subset of neurofibrillary tangles and not with neuropil threads or dystrophic neurites. Detection of the presenilin epitope in neurofibrillary tangles was observed in sporadic **Alzheimer**'s disease brain samples and in samples from individuals carrying PS-1 and PS-2 mutations with no qualitative difference. These data indicate that both wild-type and mutant PS **proteins** are involved in a common pathogenic pathway in AD.

L26 ANSWER 86 OF 98 MEDLINE DUPLICATE 34
97060735 Document Number: 97060735. Structure and alternative splicing of the **presenilin-2** gene. Prihar G; Fuldner R A; Perez-Tur J; Lincoln S; Duff K; Crook R; Hardy J; Philips C A; Venter C; Talbot C; Clark R F; Goate A; Li J; Potter H; Karran E; Roberts G W; Hutton M; Adams M D. (Suncoast Alzheimer's Disease Laboratories, Department of Psychiatry, University of South Florida, Tampa 33613, USA.)
NEUROREPORT, (1996 Jul 8) 7 (10) 1680-4. Journal code: A6M. ISSN: 0959-4965. Pub. country: ENGLAND: United Kingdom. Language: English.
AB Missense mutations in the presenilin-1 (PS-1) and **presenilin-2** (PS-2) genes have been shown to be causes of autosomal dominant **Alzheimer**'s disease (the AD3 and AD4 loci, respectively). Alternative splicing has previously been reported in the PS-1 gene. In this study, elucidation of intron/exon boundary **sequences** revealed that PS-2 is encoded by 10 coding exons. In addition, PS-2 cDNA cloning and RT-PCR using RNA from a variety of normal tissues revealed the presence of alternatively spliced products. These products included species with in frame omissions of exon 8 and simultaneous omissions of exons 3 and 4.

L26 ANSWER 87 OF 98 MEDLINE DUPLICATE 35
97029239 Document Number: 97029239. The presenilin genes: a new gene family involved in **Alzheimer** disease pathology. Cruts M; Hendriks L; Van Broeckhoven C. (Laboratory of Neurogenetics, Flanders Interuniversity Institute for Biotechnology (VIB), Antwerpen, Belgium.) HUMAN MOLECULAR GENETICS, (1996) 5 Spec No 1449-55. Ref: 55. Journal code: BRC. ISSN: 0964-6906. Pub. country: ENGLAND: United Kingdom. Language: English.
AB A positional cloning approach has led to the identification of two closely related genes, the presenilins (PS), for autosomal dominant presenile **Alzheimer** disease (AD): PS-1 at 14q24.3 and PS-2 at 1q31-q42. The PS-1 gene was identified by direct cDNA selection of yeast artificial chromosomes containing the candidate chromosomal region. Subsequently, the PS-2 gene was identified due to its high **sequence** homology with PS-1 and its location within the candidate region defined by linkage studies. To date, 30 different missense mutations and one in-frame splice site mutation were described in PS-1, while only two missense mutations were detected in PS-2, suggesting that PS-1 mutations are more frequently involved in familial presenile AD. The PS transcripts encode novel **proteins** that resemble integral transmembrane **proteins** of roughly 450 amino acids and at least seven transmembrane domains. The genomic organization of the PS genes is very similar showing that full length PS-1 and PS-2 are encoded by 10 exons. However, different alternative splicing patterns have been observed for PS-1 and PS-2 indicating that the corresponding **proteins** (ps-1 and ps-2) may

have similar but not identical biological functions.

L26 ANSWER 88 OF 98 MEDLINE
96347710 Document Number: 96347710. STM-2, a candidate gene for the familiar
Alzheimer's disease on chromosome 1. Oshima J; Schellenberg G D. (Department of Pathology, University of Washington, Seattle 98195, USA.) TANPAKUSHITSU KAKUSAN KOSO. PROTEIN, NUCLEIC ACID, ENZYME, (1996 Aug) 41 (10) 1448-52. Ref: 28. Journal code: Q7D. ISSN: 0039-9450. Pub. country: Japan. Language: Japanese.

L26 ANSWER 89 OF 98 BIOSIS COPYRIGHT 2000 BIOSIS
1996:551332 Document No.: PREV199699273688. Localization of **presenilin -2** RNA in rat brain by in situ hybridization. Benkovic, S. A.; Morgan, D. G.; Gordon, M. N.. Dep. Pharmacol. Therapeutics, Univ. South Florida, Tampa, FL 33612-4799 USA. Society for Neuroscience Abstracts, (1996) Vol. 22, No. 1-3, pp. 1175. Meeting Info.: 26th Annual Meeting of the Society for Neuroscience Washington, D.C., USA November 16-21, 1996 ISSN: 0190-5295. Language: English.

L26 ANSWER 90 OF 98 MEDLINE
97092712 Document Number: 97092712. Membrane topology of the C. elegans SEL-12 presenilin. Li X; Greenwald I. (Integrated Program in Cellular, Molecular, and Biophysical Studies, Columbia University, College of Physicians and Surgeons, New York, New York 10032, USA.) NEURON, (1996 Nov) 17 (5) 1015-21. Journal code: AN8. ISSN: 0896-6273. Pub. country: United States. Language: English.
AB Mutant presenilins cause **Alzheimer**'s disease. Presenilins have multiple hydrophobic regions that could theoretically span a membrane, and
a knowledge of the membrane topology is crucial for deducing the mechanism
of presenilin function. By analyzing the activity of beta-galactosidase hybrid **proteins** expressed in C. elegans, we show that the C. elegans SEL-12 presenilin has eight transmembrane domains and that there is a cleavage site after the sixth transmembrane domain. We examine the presenilin **sequence** in view of the predicted topology and discuss possible mechanisms for presenilin function.

L26 ANSWER 91 OF 98 MEDLINE DUPLICATE 36
96414307 Document Number: 96414307. **Alzheimer**'s disease associated with mutations in **presenilin 2** is rare and variably penetrant. Sherrington R; Froelich S; Sorbi S; Campion D; Chi H; Rogaeva E
A; Levesque G; Rogaev E I; Lin C; Liang Y; Ikeda M; Mar L; Brice A; Agid Y; Percy M E; Clerget-Darpoux F; Piacentini S; Marcon G; Nacmias B; Amaducci L; Frebourg T; Lannfelt L; **Rommens J M; St George-Hyslop P H**. (Department of Medicine, University of Toronto, Ontario, Canada.) HUMAN MOLECULAR GENETICS, (1996 Jul) 5 (7) 985-8. Journal code: BRC. ISSN: 0964-6906. Pub. country: ENGLAND: United Kingdom.
Language: English.
AB Missense mutations in the **presenilin 2** (PS-2) gene on chromosome 1 were sought by direct nucleotide **sequence** analysis of the open reading frame of 60 pedigrees with familial **Alzheimer** 's disease (FAD). In the majority of these pedigrees, PS-1 and beta-amyloid precursor **protein** (beta APP) gene mutations had been excluded. While no additional PS-2 pathogenic mutations were detected, four silent nucleotide substitutions and alternative splicing of
nucleotides 1338-1340 (Glu325) were observed. Analysis of additional

members of a pedigree known to segregate a Met239Val mutation in PS-2 revealed that the age of onset of symptoms is highly variable (range 45-88 years). This variability is not attributable to differences in ApoE genotypes. These results suggest (i) that, in contrast to mutations in PS-1, mutations in PS-2 are a relatively rare cause of FAD; (ii) that other genetic or environmental factor modify the AD phenotype associated with PS-2 mutations; and (iii) that still other FAD susceptibility genes remain to be identified.

L26 ANSWER 92 OF 98 MEDLINE

97127732 Document Number: 97127732. The **Alzheimer**'s disease-associated presenilins are differentially phosphorylated **proteins** located predominantly within the endoplasmic reticulum. Walter J; Capell A; Grunberg J; Pesold B; Schindzielorz A; Prior R; Podlisny M B; **Fraser P**; **Hyslop P S**; Selkoe D J; Haass C. (Central Institute of Mental Health, Department of Molecular Biology, Mannheim, Germany.) MOLECULAR MEDICINE, (1996 Nov) 2 (6) 673-91. Journal code: CG3. ISSN: 1076-1551. Pub. country: United States. Language: English.

AB BACKGROUND: **Alzheimer**'s disease (AD) is a progressive neurodegenerative disorder characterized by the deposition of extracellular senile plaques composed of amyloid beta-peptide (A beta). Whereas most cases of AD occur sporadically, about 10% of AD cases are inherited as a fully penetrant autosomal dominant trait. Mutations in the recently cloned Presenilin genes (PS-1 and PS-2) are by far the most common cause of early onset familial AD. MATERIALS AND METHODS: Cellular expression of endogenous and overexpressed PS **proteins** was analyzed by immunocytochemistry and metabolic labeling followed by immunoprecipitation. In vivo phosphorylation sites of PS **proteins** were analyzed by extensive mutagenesis. RESULTS: PS-1 as well as PS-2 **proteins** were localized predominantly within the endoplasmic reticulum (ER). However, small amounts of the PS **proteins** were detected within the Golgi compartment, where they colocalize with the beta-amyloid precursor **protein** (beta APP). The PS-2 **protein** was found to be highly phosphorylated, whereas very little phosphorylation was observed for PS-1. The selective phosphorylation of PS-2 occurs exclusively on serine residues. In vivo phosphorylation of PS-2 was mapped to serine residues 7, 9, and 19 within an acidic stretch at the N terminus, which is absent in PS-1. casein kinase (CK)-1 and CK-2 were shown to phosphorylate the N terminus of PS-2 in vitro. CONCLUSIONS: The majority of PS **proteins** were detected in the ER where little if any proteolytic processing of beta APP was reported. ER retention of PS **proteins** might occur by intramolecular aggregation. Small amounts of PS **proteins** were also detected in the Golgi where they colocalized with beta APP. This might suggest that potential interactions between PS **proteins** and beta APP could occur within the Golgi. Selective phosphorylation of PS-2 **proteins** within the acidic domain missing in PS-1 indicates differences in the biological functions and regulation of the two highly homologous **proteins**.

L26 ANSWER 93 OF 98 MEDLINE

96160372 Document Number: 96160372. **Alzheimer**-associated presenilins 1 and 2: neuronal expression in brain and localization to intracellular membranes in mammalian cells. Kovacs D M; Fausett H J; Page K J; Kim T W; Moir R D; Merriam D E; Hollister R D; Hallmark O G; Mancini R; Felsenstein K M; Hyman B T; Tanzi R E; Wasco W. (Genetics and Aging Unit, Massachusetts General Hospital-East, Harvard Medical School, Charlestown 02129, USA.) NATURE MEDICINE, (1996 Feb) 2 (2) 224-9.

Journal code: CG5. ISSN: 1078-8956. Pub. country: United States. Language:
English.
AB Mutations in two recently identified genes appear to cause the majority of
early-onset familial **Alzheimer**'s disease (FAD). These two novel genes, presenilin 1 (PS1) and **presenilin 2** (PS2) are members of an evolutionarily conserved gene family. The normal biological role(s) of the presenilins and the mechanism(s) by which the FAD-associated mutations exert their effect remain unknown. Employing in situ hybridization, we demonstrate that the expression patterns of PS1 and
PS2 in the brain are extremely similar to each other and that messages for
both are primarily detectable in neuronal populations. Immunochemical analyses indicate that PS1 and PS2 are similar in size and localized to similar intracellular compartments (endoplasmic reticulum and Golgi complex). FAD-associated mutations in PS1 and PS2 do not significantly modify either their migration patterns on SDS-polyacrylamide gel electrophoresis or their overall subcellular localization, although subtle
differences in perinuclear staining were noted for mutant PS1.

L26 ANSWER 94 OF 98 MEDLINE DUPLICATE 37
97072843 Document Number: 97072843. Apolipoprotein E and amyloidogenesis. Frangione B; Castano E M; Wisniewski T; Ghiso J; Prelli F; Vidal R. (Department of Pathology, New York University Medical Center, NY 10016, USA.) CIBA FOUNDATION SYMPOSIUM, (1996) 199 132-41; discussion 141-5. Journal code: D7X. ISSN: 0300-5208. Pub. country: Netherlands. Language: English.
AB **Alzheimer**'s amyloid beta-**protein** (A beta) is a modified, pathogenic form of a constitutive host **protein**, soluble amyloid beta-**protein** (sA beta). Both are conformational isomers encoded by the gene for the beta-amyloid precursor **protein** (APP), located on chromosome 21. sA beta and A beta have identical **sequence** but are thought to differ in their secondary structure and physicochemical properties, hence they are conformational isomers. sA beta is easily degraded, while A beta is particularly resistant. A beta has a high beta-pleated sheet content, while sA beta is thought to be more
random-coil and/or alpha-helical. A beta, unlike sA beta, adopts an amyloidogenic conformation, forms aggregates and gives rise to fibrils. Most early-onset forms of **Alzheimer**'s disease (AD) have been linked to mutations of the presenilin 1, **presenilin 2** or APP genes, located on chromosomes 14, 1 and 21, respectively. Their relationship to amyloidogenesis is being investigated. On the other hand, the major risk factor for the most common form, sporadic and familial late-onset AD, is the presence of the apoE epsilon 4 allele. Recent studies have shown that a 10 kDa C-terminal fragment of apoE is complexed to A beta in neuritic plaques and that apoE isoforms can modulate amyloid formation in vitro. Moreover, thrombin cleavage of apoE generates a similar C-terminal fragment that can form amyloid-like fibrils. Thus neuritic plaques may contain both A beta and apoE amyloid fibrils. AD can be neuropathologically defined by the presence of several interacting **proteins** that can adopt an amyloidogenic conformation. This has led us to hypothesize that in AD, amyloidosis may be reactive rather than causative.

L26 ANSWER 95 OF 98 CAPLUS COPYRIGHT 2000 ACS
1997:227701 Document No. 126:304309 **Alzheimer**'s Disease: melting pot or mosaic?. Blass, John P. (Burke Medical Research Institute, Cornell

University Medical College, White Plains, NY, 10605, USA). Alzheimer's Dis. Rev. [Electronic Publication], 1(1/2), 17-20 (English) 1996. CODEN: ADREFN. URL: http://www.coa.uky.edu/ADReview/blass.htm Publisher: Sanders-Brown Center on Aging, University of Kentucky.

AB A brief review with 18 refs. **Alzheimer**'s Disease (AD), like the proverbial elephant, can be described in a no. of ways, all of which are accurate and all of which are incomplete. AD can be described, correctly, as: a loss of synapses; a premature loss of neurons in a selectively vulnerable pattern, often assocd. with apoptosis and other mechanisms of cell death which involve free radicals; a disorder of free radical metab. ("oxidative stress"); a cerebrometabolic disease involving impaired glucose/energy metab.; a cytoskeletal disease; a form of cerebral amyloidosis; a disorder of signal transduction; a disorder of cerebral calcium homeostasis; a membrane disorder; and a disorder of neurotransmission, with prominent impairment of cholinergic function and more variable but typical involvement of other neurotransmitter systems. Mol. genetic studies to date suggest that the most important trait predisposing to the common, late onset form of AD is possession of the 4 allele of the ApoE gene. Studies in progress suggest the possibility that a genetic abnormality in a component of the Krebs tricarboxylic acid cycle (the a-ketoglutarate dehydrogenase complex) is also be important factor in the common, late onset form of AD. In the rarer, early onset familial forms of AD (FAD), the most common genetic abnormalities appear to be the presenilin-1 or **presenilin-2**-genes, which seems likely from the predicted amino acid **sequences** to lead to abnormalities in signal transduction or cellular calcium homeostasis. Abnormalities in the gene for the amyloid precursor **protein** were the first mutations assocd. with AD, but in fact have proven to be rare even in FAD.

Based on currently available data, any one of the mechanisms listed above could be proposed to be the central step in the pathophysiol. of AD, with other mechanisms acting through their effects on that "mainstream" abnormality. An alternative hypothesis is that a complex mosaic of abnormalities leads to the pattern of brain scarring which characterizes AD. Different parts of the mosaic may have or more or less important roles, depending on genetic endowment and environmental factors. Different parts of the mosaic may interact with each other. For instance, the abnormality in glucose/energy metab. in AD which the authors and others have been studying may well influence the progression of the disease by diminishing the ability of nerve cells to adapt to challenges ("stressors") created by other mechanisms which are part of AD. Precedents for this "mosaic hypothesis" include other complex degenerative diseases which are better understood than AD, such as atherosclerosis or clotting disorders.

L26 ANSWER 96 OF 98 CAPLUS COPYRIGHT 2000 ACS

1996:13923 Document No. 124:83879 Identification and expression analysis of a potential familial **Alzheimer** disease gene on chromosome 1 related to AD3. Li, Jinhe; Ma, Junli; Potter, Huntington (Dep. Neurobiol., Harvard Med. Sch., Boston, MA, 02115, USA). Proc. Natl. Acad. Sci. U. S. A., 92(26), 12180-4 (English) 1995. CODEN: PNASA6. ISSN: 0027-8424.

AB The inheritance of much early-onset **Alzheimer** disease (AD) has been linked to a dominant-acting locus on chromosome 14. Recently, the

gene likely responsible for this genetic linkage has been identified and termed AD3. Five mutations have been found in AD3 that segregate with the disease phenotype in seven AD families and are not present in unaffected individuals. Here the authors report the existence of a gene encoding a seven transmembrane domain **protein** very similar to that encoded by AD3 in structure and **sequence**. This gene is located on chromosome 1, is expressed in a variety of tissues, including brain, and is predicted to harbor mutations causing nonchromosome 14 familial AD. The presence of several S/TPXX DNA binding motifs in both the AD3 **protein** and the AD3-like **protein**/AD4 **protein** suggests a possible role in intracellular signaling and gene expression or in linking chromatin to the nuclear membrane. Ways in which mutations in either gene could lead to AD are discussed.

L26 ANSWER 97 OF 98 MEDLINE DUPLICATE 38
96352216 Document Number: 96352216. A mutation in **Alzheimer**'s disease destroying a splice acceptor site in the presenilin-1 gene. Perez-Tur J; Froelich S; Prihar G; Crook R; Baker M; Duff K; Wragg M; Busfield F; Lendon C; Clark R F; et al. (Department of Psychiatry, University of South Florida, Tampa 33613, USA.) NEUROREPORT, (1995 Dec 29) 7 (1) 297-301. Journal code: A6M. ISSN: 0959-4965. Pub. country: ENGLAND: United Kingdom. Language: English.

AB A series of mutations has been reported in the presenilin-1 (PS-1) gene which cause early onset **Alzheimer**'s disease (AD). The mutations reported to date have encoded missense mutations which alter residues conserved between PS-1 and the **presenilin-2** (PS-2) gene. We have recently determined the intron/exon structure of the PS-1 gene and this information has been used to identify a mutation in the splice acceptor site for exon 9 in a family with early onset AD. Amplification of cDNA from lymphoblasts of affected individuals revealed that the effect of the mutation was to cause splicing out of exon 9, however it does not change the open reading frame of the mRNA. The importance of this observation is discussed.

L26 ANSWER 98 OF 98 MEDLINE
96024664 Document Number: 96024664. The structure of the presenilin 1 (S182) gene and identification of six novel mutations in early onset AD families.
Alzheimer's Disease Collaborative Group. Anonymous. NATURE GENETICS, (1995 Oct) 11 (2) 219-22. Journal code: BRO. ISSN: 1061-4036. Pub. country: United States. Language: English.

AB Genetic linkage studies place a gene causing early onset familial **Alzheimer**'s disease (FAD) on chromosome 14q24.3 (refs 1-4). Five mutations within the S182 (Presenilin 1: PS-1) gene, which maps to this region, have recently been reported in several early onset FAD kindreds. We have localized the PS-1 gene to a 75 kb region and present the structure of this gene, evidence for alternative splicing and describe six novel mutations in early onset FAD pedigrees all of which alter residues conserved in the STM2 (**Presenilin 2**: PS-2) gene.

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